Investigating Neural and Behavioral Pre-Markers of Developmental Dyslexia Prior to Reading Onset

Thesis

presented to the Faculty of Arts

of

the University of Zurich

for the Degree of Doctor of Philosophy

by

Nora Maria Raschle

Citizen of Hemberg (SG)

Accepted in the fall semester 2011

on the recommendation of

Prof. Dr. rer. nat. Lutz Jäncke

Prof. Dr. rer. nat. Martin Meyer

Zurich 2011

For Noelle Marie and Kian Maximilian Raschle

Contents

ACKNOWLEDGMENT

I would like to thank everyone that has supported me during my PhD studies. I am especially grateful to my direct supervisors Prof. Lutz Jancke and Dr. Nadine Gaab, from the Universities of Zurich, Switzerland, and the Children's Hospital and Harvard Medical School, Boston (USA). I am deeply in debt for having received exceptional mentorship, guidance, advice and friendship.

My personal gratitude is going to the Laboratories of Cognitive Neuroscience at the Children's Hospital in Boston, where I have met fellow researchers with incredible personalities. Although there are many to name, one special thanks goes to my co-workers and friends Jennifer Zuk, Patrice Stering and Michelle Lee. I furthermore want to thank all the participating families that I have met during my thesis work and without whom this work would not have been possible. I would also like to acknowledge the financial support from the Swiss National Science Foundation and the Janggen-Poehn Stiftung in Switzerland. I am greatly thankful for the opportunity to stay as a visiting PhD student in Boston (USA).

Finally, I wish to thank all my friends, my family, my children and my husband, who have been there for me on every step of my life, ever since we met. Thanks to my parents, Bruno and Sieglinde Schnider, who have always supported me in all my endeavors and continue to encouraged me in pursuing my personal and professional goals. Thanks to my husband, Thomas Raschle, for showing me the world of science, for always having my back and most importantly, for entering into the most crazy, and fun adventures of live together. I have been shaped by the places we have lived, the countries we have traveled to and the people I have met. I am unbelievably grateful for the opportunities I have been given and the gifts live has presented me with. I would like to dedicate this work to my two children Noelle Marie and Kian Maximilian Raschle. They are the most adorable, curious, adventurous and hilarious children, who have shown and opened up a world to me, I have not known before. I hope that one day you will be the ones that will continue to pursue your dreams.

ABBREVIATIONS

DD, developmental dyslexia;

FHD+, children with a family-history of dyslexia;

FHD-, children without a family-history of dyslexia;

VBM, voxel-based morphometry;

DTI, diffusion tensor imaging;

RAN, rapid automatized naming;

WRMT, Woodcock Reading Mastery Test;

CELF, Clinical Evaluation of Language Fundamentals;

CTOPP, Comprehensive Test of Phonological Processing;

SES, socioeconomic status;

HLE, home literacy environment;

GMVI, gray matter volume indices;

ROI, region of interest;

LOT, left occipitotemporal area;

LTP, left temporoparietal region;

RTP, right temporoparietal region;

LFG, left fusiform gyrus;

RLG, right lingual gyrus;

MRI, magnetic resonance imaging;

NIRS, Near infrared spectroscopy;

BOLD, blood oxygenation level dependency;

DTI, diffusion tensor imaging;

FA, fractional anisotropy;

SUMMARY

Developmental dyslexia is a specific learning disability characterized by difficulties with accurate/fluent word recognition and poor decoding skills affecting up to 5-17% of all children. Dyslexia can only be diagnosed after the onset of formal reading instruction, which limits the time available for early interventions that may prevent the serious clinical, psychological and social impact of dyslexia. Pedigree studies suggest that dyslexia is highly heritable and several dyslexia candidate genes have been reported. The majority of these genes have been shown to be important for brain development.

Previous research using magnetic resonance imaging (MRI) has revealed differences in brain structure and function in children and adults with a diagnosis of dyslexia compared to typical reading controls. Reduced activations in posterior left-hemispheric dorsal and ventral reading networks have been reported to be characteristic of individuals with dyslexia compared to controls and are correlated with reduced reading skills. Furthermore, individuals with dyslexia show decreased gray matter volume indices when compared to controls in brain areas including left occipitotemporal (dorsal) and temporoparietal (ventral) brain regions, which also correlate with reading ability. However, it remains unclear when and how differences in brain functions and structure manifest. Therefore the main goal of the present thesis is the investigation of possible functional, structural and behavioral pre-markers of developmental dyslexia in children before reading onset. For the current thesis work, over 50 children (half of them with a family-history of dyslexia) were invited to participate in two behavioral and one imaging session.

Due to technical and practical challenges of imaging young children a majority of research studies utilizing magnetic resonance imaging have been done in school-aged children and older. The first two studies (**studies 1 and 2**) reported in this thesis were designed to develop new and modify existing pediatric neuroimaging protocol to allow neuroimaging in infants or children as young as four years of age. The described protocol allowed us to perform over a hundred successful neuroimaging sessions in children aged four years and up. In a second part of the

presented work (**studies 3 to 5**) we aimed to investigate previously seen disruptions in structural and functional networks of individuals with developmental dyslexia in pre-reading children at risk. Functional neuroimaging results revealed reduced activation patterns in occipitotemporal and temporoparietal brain areas during phonological processing in pre-reading children at risk for dyslexia when compared to typical developing controls. Additionally, there is a disruption of neural networks of rapid auditory processing in left prefrontal brain regions, similar to that seen in individuals with a diagnosis of dyslexia. Our findings have been complemented by structural results in pre-reading children at risk for dyslexia. Voxel-based morphometry (VBM) revealed differences in gray matter volume indices in temporoparietal and occipitotemporal brain areas in children with compared to without a family-history of dyslexia prior to reading onset. The identified structural and functional characteristics of pre-reading children at risk for developmental dyslexia furthermore correlate with pre-reading skills, such as phonological processing and rapid automatized naming.

Our results show that pre-reading children at risk for dyslexia already display structural and functional alterations in brain regions that can differentiate adults and children with a diagnosis of developmental dyslexia from typical reading controls. All the children were still pre-readers at the time of testing, which suggests that the observed structural and functional differences most likely develop during the first few years of life or may already be present at birth and thus cannot be a result of failing/succeeding to read. Further studies employing longitudinal designs will have to determine whether and how the observed structural, functional and behavioral differences in children at risk for developmental dyslexia may serve as early markers for reading disabilities. The identification of early pre-markers of dyslexia in pre-reading children is essential for the development and improvement of early intervention programs and may prevent the clinical, psychological and social impact associated with developmental dyslexia.

ZUSAMMENFASSUNG

Entwicklungsbedingte Dyslexie (Lese-, Rechtschreibstörung) ist eine spezifische Lernschwierigkeit, die durch Schwierigkeiten mit akkurater und flüssiger Wort-Identifikation und mangelhaftem Leseverständnis gekennzeichnet ist. Dyslexie betrifft etwa 5-17% aller Kinder und kann erst nach Beginn des offiziellen Leseunterrichtes diagnostiziert werden. Eine späte Diagnosestellung verhindert den frühzeitigen Interventionsbeginn was gravierende klinische, psychologische und soziale Folgen unterbinden könnte. Stammbaum Studien weisen auf die hohe Erblichkeit von Dyslexie hin. Es wurden zudem bereits mehrere Gene gefunden, welche mit Dyslexie in Verbindung gebracht werden. Die Mehrheit dieser Gene spielen während der Entwicklung des menschlichen Gehirns eine bedeutende Rolle.

Wissenschaftliche Studien konnten bereits zeigen, dass sich Gehirnfunktionen sowie -strukturen von Kindern und Erwachsenen mit Dyslexie von denjenigen typisch lesender Kontrollgruppen unterscheiden lassen können. Mit Hilfe von Techniken wie der Magnetresonanz-Tomographie (MRT) wurde bei Kindern und Erwachsenen mit Dyslexie eine verminderte Aktivierung in den posterior dorsalen und ventralen Lesezentren der linken Hemisphäre gemessen. Das Ausmass der neuronalen Aktivierung in diesen Hirngebieten korreliert zudem mit Fähigkeiten, die zur Leseentwicklung beitragen (z.B. phonologische Verarbeitung). Zudem konnte in den Gehirnen von Menschen mit einer Dyslexie-Diagnose eine Reduktion des Volumens der grauen Substanz in den okzipitotemporalen (dorsal) und temporoparietalen (ventral) Arealen festgestellt werden. Das Volumen der grauen Substanz in den Lesezentren der linken Hemisphaere korreliert wiederum mit auditorischer und phonologischer Verarbeitung. Die genaueren Umstände über das zeitliche Auftreten und die Ursache dieser Unterschiede in Gehirn Struktur und Funktion bleiben jedoch weitgehend unbekannt. Die vorliegende Doktoratsarbeit zielt darauf ab, funktionelle, strukturelle oder behaviorale Vorzeichen von Dyslexie zu untersuchen. Zu diesem Zweck wurden über 50 Vorschulkinder (27 davon mit einer familiären Belastung von Dyslexie), welche noch nicht zu lesen begonnen haben, zu zwei behavioralen und einer MRT- Untersuchung eingeladen.

Aufgrund technischer und praktischer Schwierigkeiten beschränkten sich wissenschaftliche MRT-Untersuchungen bisher mehrheitlich auf Erwachsene, Jugendliche und Schulkinder. Die ersten beiden Studien (**Studie 1 und 2**) dieser Doktoratsarbeit widmen sich deshalb dem Thema der pädiatrischen Bildgebung. Ziel dieser Untersuchungen war die Modifizierung bestehender und Entwicklung neuer Protokolle, welche MRT Untersuchungen an Neugeborenen und/oder Kindern im Vorschulalter ermöglichen. Im Rahmen dieser Doktorarbeit, konnten Dank des neu entwickelten Prokolls über hundert erfolgreiche MRT-Untersuchungen an Kindern zwischen dem vierten und sechsten Lebensjahr durchgeführt werden. Ein zweiter Teil der vorliegenden Dissertation (**Studien 3 bis 5**) bezieht sich auf die Untersuchung struktureller und funktioneller Lesenetzwerke bei Kindern mit und ohne familiäre Belastung von Dyslexie vor Lesebeginn. Die Resultate der funktionellen Bildgebung zeigen, dass Vorschulkinder mit einem Risiko für Dyslexie während der phonologischen Verarbeitung eine reduzierte Hirnaktivität in okzipitotemporalen und temporoparietalen Arealen im aufweisen. Des Weiteren konnte bei Kindern mit einer Familiengeschichte von Dyslexie bei der Verarbeitung von schnellen akustischen Reizen eine Störung des neuronalen Netzwerks in den präfrontalen Hirnregionen der linken Hemisphäre festgestellt werden. Diese Ergebnisse stimmen mit Befunden von Menschen mit diagnostizierter Dyslexie überein. Die hier gefundenen funktionellen Unterschiede zwischen Kindern mit und ohne Dyslexie-Risiko vor Lesebeginn werden durch strukturelle Resultate bestätigt. Die strukturelle MRT-Resultate zeigen eine Reduktion der grauen Hirnsubstanz in temporoparietalen und okzipitotemporalen Hirnarealen auf. Areale mit identifizierten strukturellen und funtionellen Defiziten in Kindern mit Dyslexie Risiko koennen mit sprachlichen Vorkenntnissen in Bezug gebracht werden, welche für die Leseentwicklung wichtig sind.

Unsere Resultate zeigen, dass bereits vor Lesebeginn im menschlichen Gehirn Signaturen struktureller, funktioneller und verhaltensbezogener Unterschiede zwischen Kindern mit und ohne Dyslexie Risiko gefunden werden können. Dies entspricht Befunden aus Studien mit älteren Kindern und Erwachsenen, welche bereits als Dyslektiker diagnostiziert wurden. Zum Zeitpunkt der vorliegenden Untersuchungen hat keines der teilnehmenden Kinder bereits zu

lesen begonnen. Dies lässt die Schlussfolgerung zu, dass die gefundenen Unterschiede sich entweder in den ersten Lebensjahren entwickelten oder bereits bei Geburt vorhanden sind. Die vorliegenden Resultate können deshalb keine Folge einer Leseschwierigkeit per se sein, sondern sind mögliche Vorläufer einer Lese-/Rechtschreibschwierigkeit. Künftige Langzeitstudien werden zu untersuchen haben, ob und wie die gefundenen Unterschiede für eine frühzeitige Dyslexie-Identifikation oder Risikoabschätzung genutzt werden können. Die frühzeitige Erkennung von Kindern mit Lese-/Rechtschreibschwaechen ist entscheidend für die Entwicklung neuer und die Modifikation bestehender Interventionsprogramme und könnte die assoziierten negativen psychologischen, sozialen und klinischen Konsequenzen vermindern oder gar eliminieren.

1 INTRODUCTION

1.1 READING, READING DEVELOPMENT AND THE STUDY OF READING DISABILITIES

The famous American author James Carroll once stated that *"Reading is an act of interiority, pure and simple. Its object is not the mere consumption of information….Rather, reading is the occasion of the occasion of the encounter with the self….The book is the best thing human beings have done yet."* Reading is one of the most (if not the most) important inventions that human beings have ever created. Invented only a few thousand years ago (McCandliss et al., 2003) it has shaped our culture as well as rearranged our brains, expanding the way we think (Wolf, 2007).

Reading is a complex skill usually learned through extensive practice and repetition. The ability to read involves many different abilities (e.g. phonological processing, rapid auditory naming, etc.) leading to adequate language comprehension as well as fluent word identification (Vellutino et al., 2004). In light of its complexity and the various cognitive processes involved during reading acquisition, it is not surprising that there have always been those who struggle with reading and the accurate acquisition of this challenging skill. Looking at the omnipresence of print in our everyday lives, the challenges individuals with reading disabilities face and its implications become obvious.

To date, there is a long line of research looking at reading, reading acquisition and reading failure. Scientific studies of reading acquisition have, for example, taught us that by birth, some of the language skills that later become crucial for reading are already present or in early developing stages (Lundberg, 2002, Friederici, 2006). Studies in pregnant woman indicate that infants in-utero are already able to discriminate between different sound structures (Groome et al., 2000). Similarly, infants are believed to be able to distinguish the sentence melody (prosody) of their mother tongue (Lundberg, 2002, Friederici, 2006). Learning to read depends on the acquisition of various sub-skills, which in turn depend on an infants' general cognitive

skills development (Vellutino et al., 2004). It is argued that a basic organizing principle of the language and reading networks, their organization within the left hemisphere, is already apparent between birth and three months (Dehaene-Lambertz et al., 2002).

Reading abilities are thought to emerge from preexisting visual perception and language abilities (Schlaggar and McCandliss, 2007) which can be identified in children as young as a few months of age. For example, a basic knowledge of the rules that compound our spoken and written language can already be detected around 30 months of age (Friederici, 2006). Newborns are furthermore capable of distinguishing any phonetic contrast (e.g. (Mehler et al., 1994)), an ability that disappears after a few months of life (e.g. (Werker and Tees, 1984)). Early auditory processing skills are said to provide the foundation for one of the main skills directly linked to reading acquisition, namely the ability for grapheme-phoneme mapping (phonological processing; (Share, 1995, Schlaggar and McCandliss, 2007)). In order to understand language, a child has first to understand that spoken language is comprised of a variety of different sounds. For example, in order to discriminate phonemes a child needs the ability to detect small changes in sounds, defined by differences in auditory frequency and intensity. As such, the syllables /ba/ and /da/ can be distinguished only by the initial 40-ms of the sound waveform (Tallal, 2004). The ability to unscramble spoken language into its smallest parts (phonemes) is crucial for being able to later on map print (orthography) to spoken language (phonology).

Extensive research has revealed a whole range of linguistic pre-cursors of later reading ability, including phonological processing (Stanovich and Siegel, 1994, Nation and Hulme, 1997, Pennington and Lefly, 2001, Snowling, 2003, Flax et al., 2009), speech perception (Pennington and Lefly, 2001, Flax et al., 2009), syntax production and comprehension (Silva et al., 1985, Share et al., 1989, Tunmer, 1989, Butler et al., 2001), language comprehension (Flax et al., 2009), object naming (Wolf and Goodglass, 1986, Share et al., 1989), receptive vocabulary (Share et al., 1989, Stanovich and Siegel, 1994) and rapid automatized naming abilities (Lundberg et al., 1980, Mann and Liberman, 1984, Pennington and Lefly, 2001). Phonemic representations such as the knowledge about syllables, onsets, and rimes are ideally acquired

before reading onset. Current research further suggests that the acquisition of phonological awareness skills is language universal (Goswami, 2000).

Through intensive practice and through various contributing factors (Turkeltaub et al., 2003), the developing reader learns to connect letters to words, and words to a text. When the ability to read accurately is mastered, reading development reaches its final stages which include fluent reading ability as well as comprehension of the read material. Fluent reading is accomplished when a text can be read accurately and rapidly, but also when clarity of expression is gained (Shaywitz and Shaywitz, 2008). Computational models of reading have thought to visualize the complex processes and interactions involved during reading and reading acquisition (Coltheart et al., 2001, Perry et al., 2007, Ziegler et al., 2008). One of the most prominent current models explaining literacy acquisition is the dual route model of reading (Coltheart et al., 2001). This model suggests that accurate reading is achieved through two major routes: the lexical (orthographic) route for known irregular words and the non-lexical (phonological) route for novel words and non-words. According to the dual route model of reading, fluent reading can only be achieved through the concise interplay of attentional, visual and low-level orthographic processing (Coltheart et al., 2001, Ziegler et al., 2008).

Research studies investigating the behavioral and neural mechanisms involved in reading and reading acquisition have been complemented by research looking at those who fail learning to read. Cognitive skills imperative for successful reading acquisition (e.g. phonological processing, the ability to map print to spoken language; or rapid auditory processing, the ability to discriminate small changes in sounds as for example within consonant-vowel-consonant speech sounds) have shown to be impaired in individuals with reading disabilities (e.g. (Tallal, 1980b, Snowling, 2000)) and neural systems for reading have shown to be disrupted (e.g. (Shaywitz et al., 1998b, Shaywitz et al., 2004a)). Any model and pre-cursor of successful reading acquisition is therefore validated by findings in individuals with reading disabilities, such as dyslexia.

1.2 DEVELOPMENTAL DYSLEXIA – DEFINITIONS AND CURRENT VIEW

Developmental Dyslexia, historically referred to as 'congenital word blindness' (Morgan, 1896), is a specific, significant reading disability affecting approximately 5-17% of all school aged children (Shaywitz, 1998b). It is considered to occur along a continuum, where reading disabilities represent the low end of a normal distribution (Shaywitz and Shaywitz, 2005). Developmental dyslexia is amongst the most prevalent and frequently studied developmental disabilities (Beitchman et al., 1986, Shaywitz et al., 1990). It is characterized by a weakness with accurate and/or fluent word recognition, poor spelling and decoding performance and is disproportionate to other cognitive abilities, such as IQ. It cannot be explained by poor vision, hearing or a lack of education or motivation (Critchley, 1970, World Health Organization, 1992). Epidemiologic longitudinal studies indicate that developmental dyslexia constitutes a chronic syndrome which cannot be attributed to a transient developmental delay (Shaywitz and Shaywitz, 2005).

A clinical diagnosis for developmental dyslexia usually derives from a standardized psychometric testing session. Most people consider a discrepancy between general intelligence [average or above average] and measures of reading [ranging 1-2 standard deviations below average] is typical for children and adults with a diagnosis of dyslexia. This is in line with notions that reading disabilities are independent from any other talents (von Karolyi et al., 2003); in fact there are reports of studies showing an increase in abilities such as visual spatial abilities (von Karolyi et al., 2003).

Most researchers agree that difficulties in phonological processing represent the most robust characteristics of developmental dyslexia, which can persist throughout adolescence (Felton et al., 1990, Lyon, 1995) and into adulthood (Felton et al., 1990, Vogel and Adelman, 1992, Shaywitz et al., 1999a). However, it remains unknown whether phonological processing deficits constitute a so called 'core deficit' or whether such difficulties may be caused by various underlying processes. Pure phonological processing models have dominated the field of developmental dyslexia research for a long time. These theories assume that a deficit in

phonological representations and phonological processing impairs the ability to access representations of phonemes, and associate them with graphemes (Ramus, 2003). Widespread evidence that most dyslexics have difficulties in at least three types of tasks including phoneme awareness (Wagner and Torgesen, 1987, Montgomery and Windsor, 2007, Kovelman et al., 2011), verbal short-term memory (Mann and Liberman, 1984) and rapid automatized naming (Wolf and Goodglass, 1986, Nicolson and Fawcett, 1990, Montgomery and Windsor, 2007) supports this line of research. However, pure phonological processing theories cannot account for the full range of symptoms experienced by individuals with developmental dyslexia, who pertain to experience additional subtle deficits within the visual (Eden et al., 1996a, Eden et al., 1996b, Grinter et al., 2010, Lipowska et al., 2011), auditory (Gaab et al., 2007, Stefanics et al., 2011) and motor area (Stoodley et al., 2006, Brookes et al., 2010). As early as 1937, Samuel Orton suggested that children with reading disabilities may have a perceptual impairment (Orton, 1937). Since then, a range of alternative theories have been suggested. An overview about some of the most prevalent theories is given in **Box 1**. One prominent example of an alternative theory, which is not based on phonological processing as a single core deficit, is the double deficit theory of developmental dyslexia (Wolf and Bowers, 1999). This theory is based on the observation that many individuals with developmental dyslexia demonstrate a weakness in rapid automatized naming tasks (or naming-speed deficits; e.g. (Grigorenko et al., 1997, Wolf and Bowers, 1999, Wolf and Bowers, 2000, Arns et al., 2007)). Reviewing cross-sectional, longitudinal and cross-linguistic studies the authors suggest that developmental dyslexia may in fact be caused by two independent mechanisms (a double deficit): deficits in (**i**) phonological processing and (**ii**) naming-speed. According to this theory, it is possible to separate individuals with dyslexia into those who have deficits in phonological processing, those who have deficits in naming-speed and a third group demonstrating both deficit (Wolf and Bowers, 1999).

Box 1. Dyslexia Theories.

(I) **The phonological processing theory** (deficit in the ability to manipulate speech sounds of language): This theory assumes that a deficit in phonological representations and processing impairs the ability to access representations of phonemes, and associate them with graphemes. This hypothesis is supported by widespread evidence that throughout studies and languages, the core deficit of individuals with dyslexia seem to be difficulties in mapping print to spoken language (grapheme-phoneme mapping or phonological processing (Ramus et al., 2003)).

(II) **The rapid auditory processing theory** (deficit in rapid auditory temporal processing, e.g. discrimination of artificial syllables): Although most researchers agree that a phonological deficit is most likely proximal cause of dyslexia, it is debated whether the deficit is specific to the phonological system or whether it is secondary to a more basic auditory impairment. It needs to be further examined, whether auditory disorders are restricted to only a subset or all dyslexics and what the relation to phonological processing is (Tallal, 1980a, Ramus et al., 2003).

(III) **The visual deficit theory of dyslexia:** This theory is based on the observation that individuals with developmental dyslexia seem to be impaired on a number of visual tasks involving visuomotor, visuospatial, and visual motion processing. Disruption of the so called V5/MT areas within the brain are thought to interfere with reentrant signals to other visual cortical areas (particularly V1/V2) as well as to the oculomotor apparatus. This would offer one explanation for the oculomotor abnormalities, as the mismatch between retinal signals and cortical signals (from V5/MT) could result in inappropriate eye movements (Eden et al., 1996b).

(IV) **The cerebellar theory** (alterations of the cerebellum): Specific behavioral and neuroimaging tests indicate that dyslexia may be associated with cerebellar impairment. This theory proposes that an abnormal cerebellar development may cause the impairments in reading and writing characteristic of dyslexia, a view consistent with the recently appreciated role of the cerebellum in language-related skills (Nicolson et al., 2001).

(V) **The magnocellular theory** (reduction in magnocellular layers within the thalamus): This theory is based on knowledge that the visual magnocellular system is responsible for timing visual events when reading. Sensitivity to visual motion helps determining how well orthographic skill can develop in both good and bad readers. The theory assumes, that in dyslexics, the development of the visual magnocellular system is impaired, most likely due to impaired development of the magnocellular layers of the lateral geniculate nucleus of the brain, which reduces motion sensitivity (Stein, 2001).

(VI) **The double-deficit theory (deficit in phonological processing and/or naming speed):** This theory is based on the observations that there are many dyslexics presenting a naming speed deficit, only in some cases combined with a deficit in phonological processing. Therefore, it is suggested that there may be two core deficits, leading to three possible cases: individuals who have (**i**) a deficit in phonological processing, (**ii**) deficits in naming-speed, (**iii**) individuals with a double-deficit (impairments in naming-speed and phonological processing) (Wolf and Bowers, 1999).

(For a detailed discussion see also Ramus et al., 2003)

1.3 BEHAVIORAL BASIS OF DYSLEXIA

1.3.1 PHONOLOGICAL PROCESSING

Phonological processing describes the awareness of and ability to manipulate phonological structures. For example during an elision task a child may be asked to "Say *farm*. Now say *farm* without saying /f/" (Example based on the Comprehensive Test of Phonological Processing, CTOPP; (Wagner et al., 1999)). The majority of clinicians, reading specialists and researchers agree that developmental dyslexia originates from a central deficit within the language system (Reason, 2001, Lyon et al., 2003). Specifically, children and adults with a diagnosis of dyslexia oftentimes struggle to access the underlying sound structure of words and fail to map these to their written counterparts (e.g. grapheme-phoneme mapping) (Wagner and Torgesen, 1987, Liberman et al., 1989, Ramus, 2003). Phonological processing deficits and the inability to automatize reading, appears to be a universal characteristic of dyslexia even though there is a connection between language characteristics and aetiology (Grigorenko, 2001). In support of this, phonological processing skills are amongst the most reliable markers of later reading ability and have been the focus of intensive research (Lundberg et al., 1980, Mann and Liberman, 1984, Stuart and Coltheart, 1988, Tunmer, 1989, Stanovich and Siegel, 1994, Nation and Hulme, 1997, Burgess and Lonigan, 1998, Pennington and Lefly, 2001, Snowling, 2003, Flax et al., 2009). For example Pennington and Lefly (2001) followed middle- to upper-middle-class preschool children for three years and could show that children that were later diagnosed with a reading disability already showed low phonological processing skills before kindergarten onset (Pennington and Lefly, 2001). Similarly, the importance of early phonological processing skills during reading development was demonstrated through a longitudinal study by Burgess & Lonigan (1998). By assessing the relation between phonological sensitivity and letter knowledge in four to five year olds, it was demonstrated that a reciprocal relation between reading and phonological abilities is already present prior to reading instructions (Burgess and Lonigan, 1998). Additionally, children who enter first grade with a weak knowledge of phonemic awareness skills are more likely to develop reading difficulties compared to their average-skilled

classmates. Up to 80% of all children who are weak readers at school entry, are still classified as such in fourth grade (Juel, 1988). A weakness in phonological processing continues to characterize individuals with dyslexia, even after entering adolescence. As such, the ability of retrieving, manipulating and mapping the sounds of language is the best discriminator between children and adults with developmental dyslexia when compared to typical reading controls (Shaywitz et al., 1999b). Across various research studies, but also languages, phonological processing skills have unraveled to be the most robust connection to reading and spelling development (Goswami, 2000).

1.3.2 RAPID AUDITORY PROCESSING

Although consensus exists that developmental dyslexia is a specific language disorder with a characterized weakness in phonological processing, the proximate cause of this deficit is still debated. It has been suggested that difficulties in phonological processing may be caused by a more fundamental underlying deficit (Valas, 1999, Ahissar et al., 2000, Tallal and Gaab, 2006, Gaab et al., 2007), such as the inability to discriminate rapid changes in the sound structure of language (McArthur and Bishop, 2001, Tallal, 2004, Tallal and Gaab, 2006). Language perception is fundamentally based on the ability to manipulate, discriminate, sequence or remember rapidly presented stimuli that differ in their acoustic frequency only. Several studies show that individuals with developmental dyslexia show a significant impairment when presented with a wide range of experimental tasks involving rapid changes in sound (Ramus, 2003, Tallal, 2004, Tallal and Gaab, 2006). A multiple case study including 16 individuals with dyslexia, revealed that about 63% of all participants with reading impairments displayed auditory deficits (Ramus et al., 2003). Reviewing ten studies in which individual subject data was analyzed or displayed, Ramus et al. (2003) conclude that 39% of all dyslexic subjects that were tested, also displayed an auditory deficit. Around 1970, Tallal and Piercy (Tallal and Piercy, 1973b, a, 1974, 1975, Tallal et al., 1993) studied 6 to 9 year old children with specific language impairment (SLI) in their ability to process sequences of rapidly occurring tones. Children with SLI performed significantly lower on tasks requiring the processing of tones which were

presented within the milliseconds range when compared to typical reading controls. These and similar studies (e.g. (Tallal, 1980a) lead to the assumption that, difficulties in rapid auditory processing may constitute a basic impairment of developmental language disorders, such as dyslexia (Tallal and Piercy, 1973b, a, 1975; Heim et al., 2010) and that it is likely, that only a subgroup of individuals with dyslexia show a deficit in auditory processing. This finding would be in favor of theories suggesting a conceptualization of developmental dyslexia into different subtypes (e.g. the so called double-deficit hypothesis; (Wolf and Bowers, 1999)).

The weakness of children with language disabilities in discriminating rapidly presented stimuli has been interpreted to contribute to the language disabilities observed (Tallal and Piercy, 1974). For example Goswami and colleagues (2002) used a multiple regression analysis on the findings of 72 children which showed a significant relation between beat detection and phonological awareness. In addition to being a significant predictor for phonological awareness skills, beat detection was found to be an even stronger predictor of reading and spelling ability (Goswami et al., 2002).

1.4 NEURONAL BASIS OF DYSLEXIA

1.4.1 READING NETWORKS IN THE TYPICAL AND ATYPICAL DEVELOPING BRAIN

Extensive research in typical reading children and adults has shed light on the neural networks involved during reading and reading acquisition. There are at least two known interrelated neural systems that are involved during reading in children as well as adults: (**I**) a dorsal or temporoparietal circuit and a (**II**) more ventral or occipitotemporal circuit. These systems have consistently found to be activated by innumerable neuroimaging studies looking at reading skills all around the world (for reviews see (Shaywitz, 1998a, Pugh et al., 2000, 2001, Jobard et al., 2003, Turkeltaub et al., 2003, Vigneau et al., 2006, Richlan et al., 2009)). It has been suggested that the more temporoparietal brain areas are involved during the analytic processes (phoneme-graphem mapping), whereas the occipitotemporal areas are more involved during word identification, necessary during fluent reading (Pugh et al., 2000).

Due to technical and practical challenges when imaging young children, research studies that focus on the brain mechanisms underlying reading acquisition in pre-school aged children remain rarer. However, cross-sectional functional magnetic resonance imaging (fMRI) studies have been used to shed light on the neuronal changes accompanying reading acquisition in the typically and atypically developing child. In an exemplary study Turkeltaub et al. (2003) examined 57 typical participants from the ages six to 22 years, without neurological or psychological family history. Their findings indicate a shift in neural activity, indicated by a progressive disengagement of right ventral extrastriate areas accompanied by an increased involvement of left frontal and temporal brain areas. Turkeltaub et al., interpreted their findings in favor of Samuel Orton's 1925 theory of reading development (Turkeltaub et al., 2003). In line with work from Shaywitz and colleagues (Shaywitz et al., 1999a, Shaywitz et al., 2004a), it seems that there is a shift in the neural networks for reading across development. Along with reading acquisition some brain areas show involvement during reading regardless of the individual's age or reading skills while others display and increase (left temporal brain regions) or decrease (right temporal areas) in neuronal activation depending on age and reading ability (Shaywitz et al., 1999a, Turkeltaub et al., 2003, Shaywitz et al., 2004a).

Converging evidence has led to the picture of a neurobiological phenotype of reading disabilities, such as dyslexia (McCandliss and Noble, 2003, Shaywitz and Shaywitz, 2008). Atypical patterns of brain activity in individuals with dyslexia during reading and reading related fMRI tasks include a disruption of ventral and dorsal reading networks. Hypoactivations in ventral and dorsal brain areas are oftentimes accompanied by hyperactivations in bilateral frontal brain regions, which has been interpreted to reflect compensatory mechanisms in challenged readers (Shaywitz et al., 1998b, Hoeft et al., 2007a, Hoeft et al., 2011). Similar neuroimaging findings derive from studies in German (Kronbichler et al., 2006) or Italian (Brambati et al., 2006) individuals with a diagnosis of dyslexia. The observed pattern thus seems to be a universal characteristic of logographic writing systems.

1.4.2 PHONOLOGICAL PROCESSING

Phonological processing skills have shown to be the most consistently found key characteristic of children and adults with a diagnosis of dyslexia. Using fMRI various studies have compared children (e.g. (Kovelman et al., 2011)) and adults (e.g. (Hoeft et al., 2007a)) with a diagnosis of dyslexia to typical reading controls during phonological processing tasks. Converging evidence points towards a hypoactivation in perisylvian (temporoparietal and occipitotemporal) brain areas in dyslexia which may be accompanied by hyperactivations in left and/or right frontal brain regions (Shaywitz et al., 1998b, Pugh et al., 2001, Hoeft et al., 2007a). The observed hyperactivation in individuals with dyslexia was suggested to reflect compensatory mechanism for the dysfunctional temporoparietal and occipitotemporal reading network (Hoeft et al., 2007a). The aforementioned findings are furthermore supported by studies looking at remediation effects in children and adults with dyslexia before and after behavioral intervention (Simos et al., 2002, Eden et al., 2004). Eden et al. (2004) investigated the neural networks of phonological processing skills in adults with dyslexia before and after an 8-week phonologically based intervention program. Performance improvements were accompanied by neural changes in bilateral parietal and perisylvian brain areas (Eden et al., 2004). Similarly, Simos and colleagues (2002) examined children aged 7 to 17 before and after 80 hours of remediation using behavioral assessments as well as fMRI. Children with dyslexia showed an increase in left-hemispheric perisylvian brain regions during a visual pseudoword rhyme task (Simos et al., 2002). Hyperactivations in dyslexia in left-hemispheric ventral and dorsal reading networks have been attributed to be characteristic of dyslexia itself, independent of reading level. This question has been elegantly addressed by comparing children with dyslexia not only to age-matched, but also reading-matched controls (which are on the same reading level, but of younger age) (Hoeft et al., 2007a).

1.4.3 RAPID AUDITORY PROCESSING

Behavioral evidence has led researchers to conclude that the phonological processing deficits identified in individuals with dyslexia may be caused by a more fundamental deficit in the basic

perceptual mechanisms that are responsible for auditory temporal information processing (e.g. (Tallal and Piercy, 1973a, 1975, Tallal et al., 1980, Boets et al., 2007)). Neurophysiological studies using EEG and MEG have demonstrated differences in speech perception and auditory temporal processing in children and adults with a diagnosis of dyslexia ((Heim et al., 2003b, a), Heim et al., 2010). Furthermore deficient neurophysiological processing has been found in infants at familial risk for dyslexia or language impairment (Molfese, 2000, Guttorm et al., 2005) and has shown to predict language skills (Choudhury and Benasich, 2011). Research studies using functional magnetic resonance imaging have reported reduced brain activation in individuals with dyslexia in left prefrontal brain regions during auditory temporal processing (Ruff et al., 2002). The left prefrontal area of the brain has also shown to be involved during the processing of rapidly changing speech and non-speech sounds (Johnsrude et al., 1997, Temple, 2002).

Using artificial speech syllables, two fMRI studies in children (Gaab et al., 2007) and adults (Temple et al., 2000) with a diagnosis of dyslexia have confirmed the importance of the left prefrontal cortex during rapid auditory processing. Typical adult readers showed brain activation within left-hemispheric prefrontal cortex during rapid auditory processing. In contrary, adults with a diagnosis of developmental dyslexia show no activation within left prefrontal brain areas during the same task. However, preliminary evidence from two participating adults points towards a possible remediation effect, implied by an increase of left prefrontal activity, after training (Temple et al., 2000). Looking at a younger population of elementary school children (average age 10.5 years) with and without a diagnosis of dyslexia, a disruption in left prefrontal brain areas during rapid auditory processing in children with dyslexia is already visible. The dysfunction in the neural circuitry for rapid auditory processing in children is similar to the impairments observed in adults with dyslexia (Temple et al., 2000). Furthermore, effective remediation has shown to partly normalize deficient neural processing of rapidly presented stimuli and is accompanied by improvements in general language and reading skills (Gaab et al., 2007).

Research studies in humans have been complemented by studies using animal models. Deficits in auditory temporal discrimination in rats have been identified and linked to neuronal migration anomalies. Furthermore, amelioration in animals with developmental anomalies supports the importance of the effects of early training intervention even further. As demonstrated in the animal model, early training with appropriate acoustic stimulation may similarly ameliorate long-term processing impairments in language-impaired children (Threlkeld et al., 2009).

1.5 HUMAN VOICE PERCEPTION AND LANGUAGE ABILITIES

The human voice is a necessary instrument of communication, carrying both speech and non-speech information. Voice perception and discrimination are crucial tools of survival for any given species on earth and it has been suggested that there are voice-specific regions in the brain of animals (e.g. located in the middle of the superior temporal plane in monkeys; (Belin, 2006, Petkov et al., 2008)) as well as human beings (superior temporal sulcus; (Belin and Zatorre, 2003, von Kriegstein et al., 2003, Kriegstein and Giraud, 2004)). Understanding speech is a complex, potentially multiple level hierarchical, process (Hickok and Poeppel, 2000). Ultimately, voice contains more than just content. It allows us to perceive speaker-specific characteristics, such as age (Hartman and Danahuer, 1976), gender (Lass et al., 1976) and emotional affect (Scherer, 1995). Correspondingly, there are areas of the brain specified for the detection of these features. For example, the right superior temporal sulcus (STS) has been shown to display increased activation compared to its left-hemispheric counterpart during the identification of voice identity (Belin et al., 2000, Belin, 2006). A functional MRI study by Von Kriegstein and colleagues indicated further that more specifically the anterior part of the right STS is involved during the processing of voice identity, by showing increased brain activation in this region of the brain during voice-identification as opposed to speech comprehension (von Kriegstein et al., 2003). Behavioral studies have demonstrated a preference of newborns for human over non-humans sounds (Ecklund-Flores and Turkewitz, 1996) and research using near infrared spectroscopy (NIRS) have implicated the involvement of bilateral superior temporal

cortex regions in 4-months old (Grossmann et al., 2010). Testing voice-recognition abilities Perrachione et al. (2011) have found behavioral evidence for impairment in voice recognition abilities in individuals with dyslexia. Since voice recognition heavily relies on linguistic features (e.g. phonology), they interpreted that the phonological processing deficits observed in children and adults with a diagnosis of dyslexia may be caused by a more general language disability (Perrachione et al., 2011).

1.6 MORPHOLOGICAL MARKERS OF DD

In 1985 Galaburda and colleagues run one of the first studies examining the brain structure of patients with dyslexia (post-mortem evaluation). Their pioneering work indicated and involvement of the left hemispheric perisylvian area as well as a cerebral asymmetry (planum temporale) in the four subjects studied (Galaburda et al., 1985). Since then, various structural magnetic resonance imaging studies using voxel-based morphometry (VBM), diffusion tensor imaging (DTI), or computer tomography (CT) have revealed differences in the brain structure between children and adults with dyslexia, compared to typical reading controls (Eckert, 2004). These areas are located within neural systems linked to language and reading (Eckert et al., 2005) which include left occipitotemporal and temporoparietal areas (Brown et al., 2001, Brambati et al., 2004, Eckert et al., 2005, Silani et al., 2005, Hoeft et al., 2007a, Kronbichler et al., 2008, Pernet et al., 2009), bilateral fusiform (Kronbichler et al., 2008) and lingual gyrus (Eckert et al., 2005) as well as the cerebellum (Brown et al., 2001, Brambati et al., 2004, Eckert et al., 2005). Additionally, gray matter volume indices in these areas are linked to (pre-)reading skills, such as timed and untimed (pseudo-) word reading (Silani et al., 2005, Kronbichler et al., 2008, Steinbrink et al., 2008, Pernet et al., 2009), phonological processing (Kronbichler et al., 2008, Pernet et al., 2009), spelling performance (Pernet et al., 2009) and rapid automatized naming (RAN) (Kronbichler et al., 2008).

Similarly, diffusion tensor imaging (DTI) studies have identified differences in the white matter structure of the brains of individuals of developmental dyslexia, again affecting the neural

subsystems of reading and language-related processes within the brain. For example DTI studies in children (Deutsch et al., 2005) and adults with dyslexia (Steinbrink et al., 2008) have revealed a significant decrease in fractional anisotropy (FA) in bilateral temporo-parietal white matter structures. These changes where furthermore associated with measures of word reading, spelling and rapid automatized naming. These findings are in line with research linking white matter atypicalities in temporo-parietal brain areas with reading ability in typical developing children (Niogi and McCandliss, 2006). Differences in white matter structure also correlate positively with reading ability, such as reading speed or word and pseudo-word reading (Klingberg et al., 2000, Silani et al., 2005, Steinbrink et al., 2008).

1.7 GENETICS, FAMILIAL RISK AND EARLY PRE-CURSORS OF DYSLEXIA

Research has shown that developmental dyslexia is highly heritable (Childs and Finucci, 1983, Pennington, 1991) and accumulating research points towards a genetic involvement in the development of dyslexia (Pennington and Smith, 1988, Pennington, 1991). In particular, epidemiologic and twin studies have supported the possibility of a biological component (Stevenson et al., 1987, Shaywitz et al., 1999a). Children who have at least one parent with a diagnosis of dyslexia are more likely to develop the disorder themselves. It has been reported that there is a dyslexia incidence rate from 23 up to 65 percent in children with at least one dyslexic parent (Scarborough, 1990, Shaywitz and Shaywitz, 2005) and a rate of about 40 percent among siblings (Pennington and Gilger, 1996 as cited in (Shaywitz and Shaywitz, 2005)). Epidemiologic studies indicate a possible gender effect, with dyslexia being more common in males then females (2:3 to 4:5; (Habib, 2000)).

Various dyslexia susceptibility genes have been reported (e.g. DYX1C1, KIAA0319, DCDC2 or ROBO1; (Galaburda et al., 2006)), some of which could be directly linked to affect brain development of language areas in the healthy human brain. For example a functional MRI study by Meda (2008) has shown that polymorphism of DCDC2 is linked to gray matter atypicalities within language-related brain areas (Meda et al., 2008). In their 2006 review work about genes

and behavior in developmental dyslexia Galaburda and colleagues (2006) conclude that variant function in genes involved in cortical development, including the previously mentioned susceptibility genes, may be causal for the subtle cortical malformations (including neuronal migration and axon growth) observed in individuals with dyslexia (Galaburda et al., 2006).

Additional evidence derives from the observation that individuals with developmental dyslexia oftentimes display comorbid deficits (e.g. dysphasia, dysgraphia, dyspraxia or hyperactivity and attention deficit disorders). This presence of various sensory deficits accompanying developmental dyslexia points towards a biological basis, which could be present before birth (genetic risk or pre-natal influences) or develop during the first few years of life (postnatal environmental influences; (Habib, 2000)).

The behavioral signature of developmental dyslexia (a language disability which is most often accompanied by deficits in phonological processing) has been extended by findings of linguistic parameters that serve as early markers of later reading ability. Linguistic pre-cursors of later reading ability include phonological processing (Stanovich and Siegel, 1994, Nation and Hulme, 1997, Pennington and Lefly, 2001, Snowling, 2003, Flax et al., 2009), speech perception (Pennington and Lefly, 2001, Flax et al., 2009), syntax production and comprehension (Silva et al., 1985, Share et al., 1989, Tunmer, 1989, Butler et al., 2001), language comprehension (Flax et al., 2009), object naming (Wolf and Goodglass, 1986, Share et al., 1989), receptive vocabulary (Share et al., 1989, Stanovich and Siegel, 1994) and rapid automatized naming abilities (Lundberg et al., 1980, Mann and Liberman, 1984, Pennington and Lefly, 2001). Behavioral findings have been complemented by studies looking at the neural correlates of (pre-)reading skills in children with and without a familial risk for using electrophysiological assessments in infants as young as a few months old (e.g. (Molfese and Molfese, 1985, Leppanen et al., 1999, Friederici, 2000, Molfese, 2000, Benaisch and Tallal, 2002, Guttorm et al., 2003, Friedrich et al., 2004, Lyytinen et al., 2004)). Additionally, variations in brain structure and function have shown to enhance the prediction of reading gains in children with a diagnosis of dyslexia (Hoeft et al., 2011). Furthermore neurophysiological (Maurer et al., 2009) and

neuroimaging measures (Hoeft et al., 2007b) have shown to add to the prediction of reading ability and dyslexia. For example Maurer and colleagues (2009) demonstrated in a 5-year longitudinal study, that EEG data and behavioral measures obtained in 6-year-old kindergarteners with and without a family history of dyslexia predicted reading outcome after reading instruction. Neurophysiological measures in kindergarten furthermore improved reading prediction in comparison to behavioral measures alone and were the only predictor for reading success in fifth grade (Maurer et al., 2009). Additionally, variations in brain structure and function (phonological processing) have been used to enhance the prediction of reading gains in middle school children with a diagnosis of dyslexia (Hoeft et al., 2011).

2 PEDIATRIC NEUROIMAGING

The advent of magnetic resonance imaging (MRI) around the 1980's has opened up new possibilities in the studies of human brain structure and function. Magnetic resonance imaging (MRI) exploits the magnetic properties of human tissue. MRI represents a tool that allows creation of images of the soft tissue of the human body while avoiding ionizing radiation, as for example the case during X-rays (Savoy, 2001). When the human brain is activated by a given cognitive process, local blood flow increases in those parts of the brain responsible for processing the demand. Functional magnetic resonance imaging (fMRI) allows researchers to plot changes in regional blood perfusion, blood volume or blood oxygenation that are thought to accompany neuronal activity (Jancke, 2005). Hereby, blood oxygenation level dependent (BOLD) fMRI is the most commonly used functional neuroimaging method in the field of cognitive neuroscience research. BOLD fMRI provides images with a high spatial resolution (within a few cubic millimeters), but a lower temporal resolution (a few seconds; limited by haemodynamic response / (Matthews and Jezzard, 2004)). To summarize the biophysics underlying the BOLD reaction, a reduction of oxygen extraction leads to an upsurge in the ratio of oxy- to deoxyhaemoglobin at the source of neural activation. BOLD fMRI is based on the detection of these regional changes in blood oxygenation levels by using the magnetic differences of haemoglobin-carrying oxygen (isomagnetic) compared to deoxygenated

haemoglobin (slightly paramagnetic) (Matthews and Jezzard, 2004). BOLD fMRI signaling reflects *relative* signal intensity changes associated with different cognitive states during a single neuroimaging session and is thus not an absolute measure of tissue metabolism. An advantage of (f)MRI in comparison to more invasive techniques, such as computer tomography (CT / using x-rays to study human anatomy), is the opportunity of MRI to be used in the serial study of one individual subjects. It is thus an optimal measure to investigate questions linked to the longitudinal study of brain development, as presented in the current thesis.

Contrary to studies in school-aged children, students and adults, MRI research in pediatric age groups is less common (Bookheimer, 2000). Practical as well as technical challenges have long restricted the extension of MRI research to younger populations (e.g. (Bookheimer, 2000, Poldrack et al., 2002)). Challenges may include procedural difficulties (e.g. participant's anxiety, movement restriction or motivation), technical complications, such as child adequate equipment (e.g. button response tools or child-sized head coils) or challenges of appropriate analysis methods (e.g. pediatric brain templates or adequate artifact detection tools). A progressive use of functional and structural MRI in younger age groups, however, could further add to our understanding of brain development. For example various cross-sectional fMRI studies have investigated the development of reading in the typical and atypically developing brain by comparing beginning and skilled readers from the age of 7-8 years (school onset) old and on (e.g. (Shaywitz et al., 1998a, Schlaggar et al., 2002, Turkeltaub et al., 2003, Brown et al., 2005, Shaywitz et al., 2007)). However, no study has yet employed a longitudinal design to study the development of reading related processes or dyslexia in pre-reading children (ages 4 and on) using fMRI. **Table 1** (pages 20 and 21) gives an overview over the different methods shown to improve the participant's compliance during neuroimaging sessions within the clinical (e.g. (Slifer et al., 1994, Tyc et al., 1995, Slifer, 1996)) or research setting (e.g.(Pressdee et al., 1997, Epstein et al., 2007)). These include play therapy (Pressdee et al., 1997), behavioral approaches (Slifer et al., 1993, Slifer et al., 1994, Tyc et al., 1995, Slifer, 1996, Byars et al., 2002, Slifer et al., 2002) and simulation (Rosenberg et al., 1997), the use of mock scanner areas (de

Amorim e Silva et al., 2006, Epstein et al., 2007), basic relaxation (Lukins et al., 1997) and a combination of these techniques (Hallowell et al., 2008).

Authors	Type [P\R]	Mock MRI	Approach	Subjects	Sex [M/F]	Age [years]	Results	Conclusion
Slifer et al., 1993	P	Y	Operant behavioral technique	4 children	[2/2]	5 to 6	significantly decreased movement through operant conditioning	These data support the use of operant conditioning to teach children to cooperate with MRI and thus avoid sedation.
Slifer et al., 1994	P		Behavioral training with motion control for radiation treatment in children without sedation	10 children		3 to 7	8 of 10 children benefit from the behavioral program	
Tyc et al., 1995	P		Cognitive-behavioural intervention in oncology patients	55 children	?	6 to 18	Reduction in distress after intervention	?
Slifer, 1996	P		Behavioral training with motion control for radiation treatment in children without sedation	11	?	?	For 9 of 11 children sedation for daily treatments could be avoided.	
Rosenberg et al., 1997	P	Y	Simulation using a mock MRI unit	32 children, 16 with obsessive compulsive disorders (OCD), 16 controls	[16/16]	6 to 17 (mean: 12.2)	significant decrease in heart rate and self-reported distress level in all subjects; all subjects successfully completed the MRI session. Subjects who were not trained in MRI trainings unit had higher hear rates and self-reported distress levels.	Simulation without pharmacological sedation successfully prepared pediatric subjects an may be an alternative procedure to sedation for MRI for children 6 years and older.
Pressdee et al., 1997	P		Play Therapy	169 children	?	4 to 8	only one of the 169 children who have been introduced to the MR environment through play therapy later needed GA	The use of play therapy has proven to be useful in reducing the needof sedation or GA in older children and is helping children to cope with their experience.
Armstrong & Aitken, 2000	P/ RA		This paper reviews the role of play preparation in pediatric anaesthesia					
Bookheimer, 2000	RA		A variety of technological, experimental, and practical aspects are reviewed when imaging children (fMRI basics, comparing groups and choosing dependent variables, regional activation patterns as dependent variables, anatomical constraints, statistical considerations, practical considerations, anesthesia and pediatric imaging). Suggestions for their management are provided. Despite the known difficulties, studying brain functions in children clearly is a growing area of research that will have a tremendous impact, both in basic science and clinical applications.					
Slifer et al., 2002	P	Y	Operant behavioral technique	4 children (2 ADHD)	[2/2]	7 to 10	accuracy increased whereas head motion decreased	Behavior analysis techniques can improve child cooperation during fMRI procedures
Byars et al., 2002	P		Systematic desensitization, orientation training	209 children	[106/103]	5 to 18 (mean: 10	overall success rate:80%, 86% of all girls and 74% of all boys completing fMRI studies	It is feasible to conduct large-scale fMRI studies of children as young as 5 years old.
Poldrack et al., 2002	RA	R	Review of methodological issues and solution which arise when performing pediatric fMRI, including compliance (minimizing anxiety, minimizing motion), data processing (motion correction, modeling motion, spatial normalization), statistical analysis and the hemodynamic response, as well as progress in pediatric fMRI (imaging basic cognitive processes, clinical fMRI, imaging neuropsychological disorders). Concluding, the use of fMRI in pediatric population continues to grow due to power, accessibility, and relative safety of the technique.					

Wilke et al., 2003	RA		An overview over current and future applications of fMRI is given, and typical problems, oitfall, and benefits of doing fMRI in pediatric age group are discussed. This is done on the background of fMRI basics, current research applicationsbrain plasticity and current clinical applications.					
Davidson et al., 2003	RA	R	Important issues relevant to developmental and clinical neuroimaging research is discussed, including anatomical, physical and psychological differences between children and adults, as well as general issues. Additionally, the development of age appropriate and scanner appropriate tasks for children are discussed, also in the context of an empirical study of development and learning in healthy children and adults.					
Sury et al., 2005	RA		This paper reviews "problems" of painless imaging (Ultrasound & echocardiography, computer tomography, nuclear medicine imaging, positron emission tomography, magnetic resonance imaging) and patient management techniques (behavioral techniques, natural sleep, sedation, anaesthesia)					
De Amorim e Silva et al., 2006	P	Y	Practice magnetic resonance unit	134 children	[63/71]	4.1 to 16.1 (mean 7.7)	This retrospective evaluation showed, that 90% of all children passed the practice session, 98% of those had a clinical non-GA MRI and 94% of those children passed.	Children as young as 4.1 years could avoid having GA or sedation for MFRI following preparation in a practice MR unit. Preparation though practice, play therapy and teaching of copying strategies is a safe and effective method to reduce the need for sedation and GA in children undergoing clinical MRI scans.
Kotsoni et al., 2006	RA	R	This issue reviews methodological and theoretical issues (developmental differences in anatomy & physiology and developmental and clinical differences i ability) and provides possible approaches (acclimation to, and modification of, the imaging environment for pediatric population) for addressing thus.					
Epstein et al., 2007	P	Y	Mock scanner compliance training Operant feedback using a video system	45 participants (23 youth, 22 parents / ADHD and non-ADHD)	[24/21]	adults: 46.9 and 47.8; youth 16.9 (ADHD) 17.6 (non ADHD)	10% data loss (excessive movement > 2mm) no in between group differences	This study illustrates the need to (1) report data attrition due to head motion, (2) assess task-related motion, and (3) consider mock scanner training in functional imaging protocols.
Hallowell et al., 2008	P	Y	(1) behavioral technique (2) use of a practice MRI unit	291 children	[142/ 149]	3.6-17 (mean 7.9)	74.9% pass at practice, 12 % borderline pass, diagnostic images from 96% of children entering MRI machine	
O'Shaughnessy et al., 2008	RA	R	This review considers principles of fMRI, issues relevant to imaging children (anatomy, development, response variability, task selection, cooperation and movement), research using fMRI to examine cognitive processing in pediatric population (executive functions, visual spatial processing, facial expression and special focus on language studies) and applications to patient care (pediatric epilepsy). Own data: it is possible to obtain reliable data in 95% of typically developing children > 8 years and 80% of children aged 4 to 5.					
Hunt & Thomas, 2008	RA	R	This review aims to provide a foundation for investigators aiming to use (f)MRI in research. Special consideration is given towards basic concepts of MRI physics, typical MRI components, scan types, experimental design factors, work with pediatric and special population.					
Thomason, 2009	RA		This gives a brief overview of some topics in pediatric neuroimaging, such as child movement and anxiety.					
Church et al., 2010	RA		This discusses and gives an overview of various issues with fMRI imaging in children. Some things discussed were assessing task performance, the "Task B problem," performance					
Henrica, MA et al., 2010	RA	Y	Confirms success rate of mock scanner use in kid fMRI studies	90 children		Total group = 3 to 14 years	For kids under 7, 33 out of 36 kids were able to continue to the fMRI session after training, and out of the 33, 23 of them had < 3mm movement in the scanner	Training protocol with a mock scanner can be applied in younger children to reduce the need for sedation.
Schlund et al., 2011	P		This talks about multiple-reward protocol involving prizes pre-selected and pre-organized by the children in a heirarchy of preference in attempt to increase task-compliance in an fMRI	28 children		9 to 13	Task complaince in the normal reward group averaged 68.4% and task compliance in the multiple reward group was 93.6%; kids in the second group also completed more of the tasks overall	This study shows that increased attention to how rewards are selected and delivered may increase cooperation rates.

3 AIMS AND RELEVANCE OF THESIS

"…The greatest terror a child can have is that he is not loved, and rejection is the hell he fears. I think everyone in the world to a large or small extent has felt rejection. And with rejection comes anger, and with anger some kind of crime in revenge for the rejection, and with crime, guilt—and there is the story of mankind…"

- John Steinbeck, East of Eden

Developmental Dyslexia is one of the most common of all developmental disabilities affecting up to one out of every five children in the United States (Shaywitz et al., 2004b). It is a specific language disability, with consequences reaching way beyond a child's classroom (Saracoglu et al., 1989, Valas, 1999, Humphrey and Mullins, 2004) or an individuals' lifespan (Marder and D'Amico, 1992, Wagner et al., 1993). Currently developmental dyslexia can only be identified around second or third grade, once children have already started to learn and, in the case of dyslexia, failed learning to read. However, ample behavioral studies provide evidence for early markers or reading ability in typical children or those with a family history of dyslexia (e.g.(Lundberg et al., 1980, Mann and Liberman, 1984, Stanovich and Siegel, 1994, Nation and Hulme, 1997, Pennington and Lefly, 2001, Snowling, 2003, Flax et al., 2009)).

To summarize, extensive research in the area of reading and reading disability has led us to the conclusion that: (**I**) Developmental dyslexia is a language based learning disability affecting about 5-17% of all school-aged children. Developmental dyslexia has been shown to run in families. Additionally, strong evidence from molecular-genetic, twin and family studies support the presence of a genetic component. (**II**) There is a characteristic behavioral phenotype, which is observable in children and adults with a diagnosis of dyslexia. (**III**) There are differences in the neural networks of children and adults with a diagnosis of dyslexia when compared to controls in reading and language-related experimental settings (in particular phonological and rapid auditory processing) (**IV**) There are differences in the brain structure (gray matter volume and white matter organization) in children and adults with a diagnosis of dyslexia compared to

typical reading controls. (**V**) Behavioral predictors for reading and reading disability can be identified in children with and without a familial risk for dyslexia prior to reading onset. (**VI**) There is initial evidence pointing towards an deficit in voice identification in individuals with dyslexia.

Although there is a lot known about the behavioral and anatomical signature of children and adults with a diagnosis of dyslexia, the current literature reveals a series of unanswered key questions regarding the development of this disability. To date it is unknown whether functional and structural brain differences observable in children and adults with a diagnosis of dyslexia are already present in children at risk for developmental dyslexia prior to reading onset. It is furthermore, unknown whether these differences could be used as early markers of reading ability and how the neural and structural signature identifiable in individuals with dyslexia develops. The current thesis work is part of a bigger longitudinal project at Children's Hospital in Boston, (Boston longitudinal study for dyslexia; BOLD) which aims to investigate early markers of later reading ability and/or dyslexia in children with and without a familial risk for dyslexia prior to school onset. The present thesis work will be a start to investigate these missing links by comprehensively characterizing brain function and structure of children with and without a family-history of dyslexia prior to reading onset. This work will furthermore lay the foundation for the first longitudinal examination of the brain development of typical developing children and those at risk for developmental dyslexia.

We have implemented a multi-level approach using functional and structural brain indices, and psychometric and psychophysical measures, which ultimately will allow us to identify the best predictor of later reading outcome. The combined assessment of brain function coupled with behavioral assessments of language and reading has been accomplished before in school-age children and adults with a diagnosis of developmental dyslexia, but to the best of our knowledge this is one of the first longitudinal studies starting to look at the behavioral, neuronal and structural phenotype of children with and without a risk for dyslexia before school-/reading-onset and follow these children for several years. Little is known about the pre-

reading brain of children with and without reading disabilities, which is partly due to practical and technical challenges when imaging very young children. Part of the current thesis work is the development and implementation of a new child imaging protocol, allowing functional and structural imaging in children as young as four years of age. Our focus on an understudied age group (pre reader to beginning readers) within the dyslexia population is highly significant and innovative as this provides an important opportunity to develop predictors for an age group where intervention might be most efficacious.

The proposed study marks the start of a bigger longitudinal project (BOLD) which will make substantial contribution to our understanding about the developmental trajectory of dyslexia. The impact of the current project is increased by the potential implications for educational practice and policy in the early intervention for developmental dyslexia. Additionally, the present research is likely to lay the foundation for a longitudinal project which will provide important information on the trajectory of normal reading development.

Therefore, the aims of the current thesis are as follows:

Aim1: *To develop an age-appropriate and child-friendly imaging protocol including the programming of child-friendly imaging tasks that address the questions under investigation.*

For findings see Empirical Part: Study 1 and Study 2

Aim2: *To test whether the neuronal correlates of phonological processing differ between children with or without a family history of DD prior to reading onset and to investigate whether there are any relations to standardized behavioral measurements*

For findings see Empirical Part: Study 3

Aim3: *To test whether the neuronal correlates of rapid auditory processing differ between children with or without a family history of DD prior to reading onset and to examine whether there are any relations to standardized behavioral measurements*

For findings see Empirical Part: Study 4

Aim4: *To examine structural differences between children with and without a family-history of dyslexia using voxel based morphometry (VBM). To test potential structure-behavior-relationships using correlational analysis.*

For findings see Empirical Part: Study 5

Aim5: *Here we aimed to investigate whether voice-specific areas in the human brain are already developed in pre-school children and whether they correspond to areas found in adolescence and adults.*

For findings see Empirical Part: Study 6

4 EMPIRICAL PART

Aim1: *To develop an age-appropriate and child-friendly imaging protocol including the programming of child-friendly imaging tasks that address the question under investigation.*

4.1 **STUDY 1:** MAKING MR IMAGING CHILD'S PLAY - PEDIATRIC NEUROIMAGING PROTOCOL, GUIDELINES AND PROCEDURE

Nora M. Raschle[1, 2], Michelle Lee[1], Roman Buechler[1], Joanna A. Christodoulou[3], Maria Chang[1], Monica Vakil[1], Patrice L. Stering[1],Nadine Gaab[1, 3, 4]
[1]Department of Developmental Medicine, Children's Hospital Boston, [2]Department of Neuropsychology, University of Zurich, [3]Graduate School of Education, Harvard University, [4]Harvard Medical School

Published in Journal of visualized experiments (JoVE; 2010).

Video document available at:

www.jove.com/details.php?id=1309 doi: 10.3791/1309.

4.1.1 ABSTRACT

Within the last decade there has been an increase in the use of structural and functional magnetic resonance imaging (fMRI) to investigate the neural basis of human perception, cognition and behavior [1, 2]. Moreover, this non-invasive imaging method has grown into a tool for clinicians and researchers to explore typical and atypical brain development. Although advances in neuroimaging tools and techniques are apparent, (f)MRI in young pediatric populations remains relatively infrequent [2]. Practical as well as technical challenges when imaging children present clinicians and research teams with a unique set of problems [3, 2]. To name just a few, the child participants are challenged by a need for motivation, alertness and cooperation. Anxiety may be an additional factor to be addressed. Researchers or clinicians need to consider time constraints, movement restriction, scanner background noise and

unfamiliarity with the MR scanner environment[2,4-10]. A progressive use of functional and structural neuroimaging in younger age groups, however, could further add to our understanding of brain development. As an example, several research groups are currently working towards early detection of developmental disorders, potentially even before children present associated behavioral characteristics [e.g.11]. Various strategies and techniques have been reported as a means to ensure comfort and cooperation of young children during neuroimaging sessions. Play therapy [12], behavioral approaches [13, 14,15, 16-18]and simulation [19], the use of mock scanner areas [20,21], basic relaxation [22] and a combination of these techniques [23] have all been shown to improve the participant's compliance and thus MRI data quality. Even more importantly, these strategies have proven to increase the comfort of families and children involved [12]. One of the main advances of such techniques for the clinical practice is the possibility of avoiding sedation or general anesthesia (GA) as a way to manage children's compliance during MR imaging sessions [19,20]. In the current video report, we present a pediatric neuroimaging protocol with guidelines and procedures that have proven to be successful to date in young children.

4.1.2 PROTOCOL

We have incorporated general experimental testing guidelines as well as MRI specific approaches [12-23] into one complete neuroimaging protocol intended to guide researchers and clinicians during neuroimaging sessions with awake children as young as four years of age. First, we aim to emphasize general testing guidelines adapted for MRI examinations. Second, we provide a hands-on, step-by-step description of our neuroimaging protocol. In our experience, a single session of approximately 2.5 hours (including a maximal imaging time of 45-60 minutes) is sufficient to train and guide a child through a neuroimaging session.

GENERAL GUIDELINES

As in every testing session with pediatric populations, general guidelines and recommendations for how best to work with young children should be considered [24]. We highlight comfort, appropriateness and motivation (**CAM**) and provide definitions of these concepts.

(C) Comfort: *Comfort is defined as the emotional state of a young participant involved in an imaging session where the feeling of threat is minimized and security is maximized.*

Environment: In line with other research groups [19,20], we consider the mock scanner area an ideal place to start a neuroimaging session. Ideally, a mock scanner area replicates the actual MRI room and MR scanner to the greatest extent possible (e.g. including a mock MR scanner mirroring an actual MR scanner's appearance and the sounds produced) [20]. This room provides the same equipment (e.g. response tools) as the actual MRI room. Without a static magnetic field, it is a safe place to familiarize the child with the imaging procedure in a child-appropriate way. The mock scanner area can be designed in a child-friendly manner by adding stuffed animals, placing a few toys in the room (not too many because this could be distracting), having parents and siblings sit on child-size chairs and table, and providing some parent-approved snacks and drinks. We further provide the child with a sticker chart, a CD with the child's structural brain images, and a treasure chest with a gift certificate and other small prizes.

Family & Friends: One way to facilitate active participation during a neuroimaging session is to encourage the participating children to invite their family, siblings and friends or to bring their own stuffed animals or toys. In addition, children and their parents should be allowed to choose whether they prefer to have one parent be present in the MRI room during the fMRI experiment.

Clothing: Clothing with no metallic pieces (e.g., buttons or zippers) is mandatory. Children may prefer to wear their own clothing. However, appropriate attire (e.g. hospital gowns) should be available if needed. As training and MRI rooms can be cold, a blanket may offer the child additional comfort.

(**A**) Appropriateness: *Appropriateness describes the framework and contexts used to present activities and materials during the neuroimaging session in relation to the age group studied.*

Terminology: The terminology and practices used during pediatric neuroimaging sessions should be carefully chosen. Doing so can avoid misconceptions or a frightening atmosphere. Inappropriate terms, for example, include the following: "*It is really loud, but it will not hurt you*" or *"How are you doing inside the machine?"*. It is recommended to use positive language that is easily understood by children and to address potential issues directly. Avoiding certain phrases can be advantageous for the session and a child-appropriate choice of technical terms is recommended (e.g. *"brain camera"* instead of *"MRI Machine"*, *"camera click"* instead of *"scanner noise"*, etc.).

Misconceptions: One important goal is to clarify the child's misconceptions about imaging as early as possible during the neuroimaging session. An easily understandable study description should be communicated prior to the visit and may be repeated at the beginning of the neuroimaging session.

Response Tools: Using specific response tools appropriate to the age of the participant has proven to be beneficial [25]. As an example, when using various instruments (e.g. headphones, response buttons, eye tracker, etc.), it is important to use those that are child-appropriate in size and shape. These instruments should be carefully positioned so that the child does not wiggle and move in an attempt to reach the response devices.

Affective State: As in every testing session, it is essential to be sensitive to the affective state of the participant. Children may not always express their feelings readily, but anxiety, boredom or frustrations need to be recognized and dealt with promptly [7,24]. Concerns need to be addressed directly and questions need to be posed in a child-appropriate manner.

Flexible Approach: It is highly recommended to account for the specific needs of each child and to allow sufficient time to make a flexible approach possible (e.g. optional help depending on the child, additional training sessions, allowing enough time for the neuroimaging session, etc.).

(M) Motivation: *Motivation describes the willingness of a participant to actively cooperate within a given research setting*

Child-Friendly Themes: We recommend using a fun theme that guides children throughout the neuroimaging session (e.g. an adventure story). By doing so, the children become invested and engaged in the sequence of the activities. Furthermore, a theme can give the research team an opportunity to build all experiments and task paradigms in a child-friendly way (e.g. using cartoon characters).

Traditional & Virtual Sticker charts: Sticker charts are well known as tools to help motivate children to complete different experiments within one session. A virtual sticker chart is analogous to the traditional sticker chart, but it can be shown (via projector) to the child when inside the MR scanner. As an example, we use a virtual sticker chart modeled after the children's game *"Chutes and Ladders"*, where the participants have to find their way home (this can only be achieved by completing the experimental tasks). Not only is this fun for the child, but it gives the research team time after each run (image acquisition time for one experimental task) to prepare for the next.

COURSE OF ACTION

Pediatric Neuroimaging Session I: Preparation

1) Before the neuroimaging session: In preparation for the neuroimaging session, the participating families are provided with information through print or online media, which contain age-appropriate descriptions offering a preview of the study content and details.

Pediatric Neuroimaging Session II: Training (approximately 1 hour)

2) Welcome & paperwork: The pediatric neuroimaging session starts in the mock scanner area, where the research team welcomes the participating child, family and friends. Institutional review board (IRB) forms (e.g., consent and assent forms), MR

scanner screening forms, and reimbursement procedures are reviewed and it is ensured that the scope of the neuroimaging session is clear for the child and the parents.

3) (f)MRI introduction: The mock scanner area is introduced to the child and the parents including a short description of the mock scanner, the response tools and additional material used during the neuroimaging session. A digital camera can be used to explain how a regular camera takes pictures and how a "brain camera" (MRI scanner) works. Examples of sharp and blurry pictures demonstrate the impact of motion on the quality of the photos or pictures (see Figure 1). Movement restriction may be illustrated through the use of optional games, such as the *"Freezing-Game"* or *"Statue-Game"*. These games require the child to stay very still (e.g. as an ice sculpture or statue) for a short period of time.

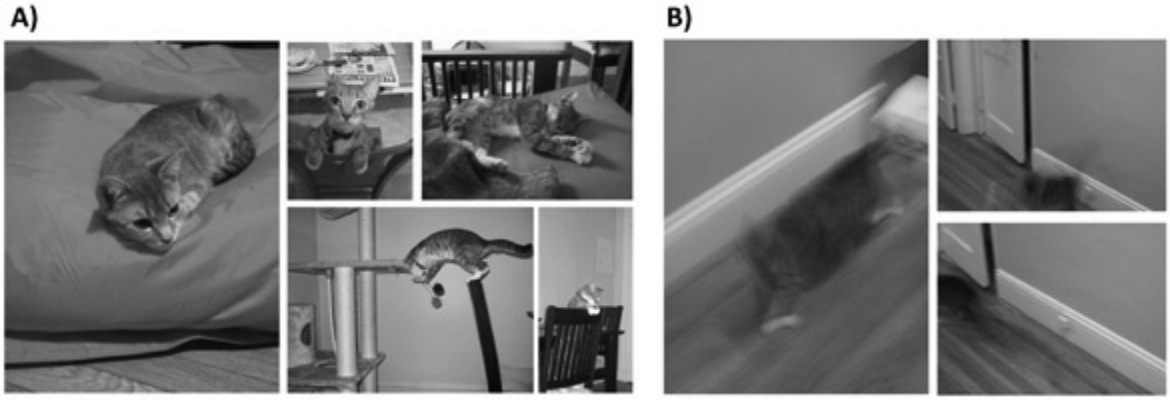

Figure 1. (A) Sharp and **(B)** blurry pictures may be used to demonstrate the impact of motion on picture quality.

4) Introduction to experiment: Before introducing the experimental tasks one can start with a short enjoyable activity. Next, the use of the mock scanner is slowly incorporated.

5.1) Short movie: For this experiment a child friendly theme is added to the neuroimaging session. The children take part in a spaceship adventure game which is introduced by a short movie; the main characters guide the child through all experiments.

5.2) Experimental tasks / "games": The use of the mock scanner is incorporated step-wise: **(1)** instructions are shown while the child is sitting on the mock scanner bed; **(2)** the instructions are repeated using printed cards which mirror a computer screen; **(3)** the first few examples are solved with the help of the research team; **(4)** training items are then presented in real time; **(5)** as a next step the child is offered the use of headphones and pre-recorded scanner background sounds are played back during the presentation of the training items; **(6)** finally, the child is allowed to play the game inside the mock scanner. The research team ensures understanding of the experimental tasks.

If using more than one response tool, such as one button in each hand, it is important to define which response tool corresponds to which answer. A child may not know the difference between left and right. A stuffed animal (e.g. a monkey) can be placed next to one side of the child. Instead of the instructions *"Press the right button"*, the instructions are changed to *"Press the monkey button"*.

5) Rules of communication: During the training the child is taught that a gentle hand press on their leg signals that they are moving too much. This signal serves as a means of communication possibility between the research team and the child during the actual fMRI experiment. It is explained to the child that speech should be avoided during image acquisition as it could interfere with the experimental task performance and impact data quality.

6) Short break / dice game: During a break, dice may be used to determine a random order in which the games will be played during the fMRI experiment. This ensures randomization across participants.

7) Repetition of main points: Before starting the fMRI experiment it is recommended that the researcher repeat the most important rules for the neuroimaging session to the child. In order to minimize memory demands on young children, it is helpful to

summarize critical information in a few main points and to reiterate those throughout the session.

8) Trouble shooting: When a child hesitates in taking part in the training session or fMRI experiment, researchers are advised to **(1)** act immediately; **(2)** offer to take a break; **(3)** address concerns and assure that participation is voluntarily; and depending on the child's choice the session is either stopped early or **(4)** game strategies as recommended by play therapists [12,26] are used to help a more anxious child get comfortable with the new environment. It is important to use flexible approaches that allow a child to participate at a pace that is comfortable for them. However, the child's choice in participation needs to be evident.

9) MRI training without mock scanner: If researchers or clinicians do not have access to a mock scanner area, game strategies as used by play therapists are highly recommended [26]. For example, a neuroimaging session can be simulated by using pictures or a model of an MR scanner [12]. Furthermore, behavioral approaches using desensitization and operant behavioral techniques [13-15,17,23] have helped to reduce distress in children and increase the number of children successfully completing their neuroimaging session.

Pediatric Neuroimaging Session III: Break and Metal Screening

10) Metal screening: Before entering the MRI room, every participant and parent must fill out and sign an MRI screening form. Additionally, the child needs to be checked for ferrous objects. A hand held metal detector or a magnet can be used to introduce the screening playfully (e.g. "pretend we are at the airport").

Pediatric Neuroimaging Session IV: fMRI Experiment (45 to 60 min)

General: During the fMRI experiment, the biggest challenge for many children is to stay very still for a long period of time. It is recommended to keep each experiment as short

as possible or to divide the experiment into two experimental runs. In our experience, run imaging times with a maximum of five to seven minutes have proven accomplishable by children elementary school age or younger. The total length of the imaging session should also be considered. However, it is easier for a child to go through a long imaging session with several short experimental runs than to complete a shorter session with longer experimental runs. Neuroimaging experiments often employ a block design in which different experimental task conditions are presented in a series of subsequent blocks. Children can easily get confused by changing task demands within one experimental run and therefore it is recommended to keeping task conditions separated (e.g., by sampling two different task conditions in two subsequent experimental runs with a break in between).

11) Facilitate transition: To facilitate the child's transition to the actual MRI room, the child is accompanied by a research staff member and may choose to bring along a parent and the child's favorite stuffed animal, as long as the toy does not contain any ferrous parts. Additionally one research team member is recommended to accompany the child.

12) Equipment check: Screen and mirror positioning (for visual experiments), sound volume (for auditory experiments), and response tools need to be checked and ear protection (e.g., ear plugs) should be provided for attendants in the MRI room. Check the response tools and settings with applied examples (e.g. play questions for the child to test audio settings and have the child answer them). The research team must ensure that every family member present in the MRI room received information on appropriate behavior and rules, especially concerning safety.

13) fMRI / experimental task performance: Task instructions should be repeated before the start of each game (experimental task). After each game, the virtual sticker chart rewards the child's cooperation. While in the MR scanner, the child's comfort and movement must be monitored. The presence of a research team member in the MRI

room has proven to be highly advantageous; the child's well-being and behavior can be observed, and essential communication and motivating feedback can be given directly to the child. Head movement of the child may be observed by the research team member present in the MRI room or by the researcher monitoring the image acquisition outside of the MRI room. A gentle hand press practiced during the training session signals to the child that they are moving too much. For experiments with several experimental runs, a short break half way through the neuroimaging session maintains comfort. As a motivational factor during the break, the child can be shown his or her own brain images.

14) Structural image acquisition: Finally structural MR image acquisition requires the participant to lie still without performing any experimental task. The child can be entertained by watching a short movie during this time. Recommended examples of appropriate movies are animal movies or documentaries as they are enjoyable and unlikely to induce laughing which may lead to head movements during image acquisition. The child handles movement restriction during the time of image acquisition more easily if told that pictures acquired during this time will be presented to them as a gift to take home, such as a CD with the child's brain pictures.

15) Closing: Once image acquisition is complete the reimbursement procedure follows including gifts, prizes and a CD with acquired brain pictures for the child to take home.

4.1.2.1 REPRESENTATIVE RESULTS

The use of appropriate preparation protocols and child-friendly imaging procedures positively influences cooperation, motivation and the experience of our participating children and their families. Use of this protocol reduces overall movement and thereby increases the chance of obtaining high quality images without the use of sedation or GA.

Using the current protocol we have recently obtained functional and structural brain imaging data for a group of pre-school aged children (ages 4.9 to 6.3 years / average age 5.5 years).

Over 95% of all children have been able to complete a neuroimaging session including mock scanner training and fMRI experiment. The guidelines and procedures presented in this protocol were designed for pediatric neuroimaging sessions. However the general principle and many of the described tools can be applied to pediatric imaging sessions in general such as image acquisition of other body parts.

4.1.3 DISCUSSION

The emergence of functional and structural MRI to study the human brain has facilitated possibilities of examining typical as well as atypical brain structure and functions and therefore holds great promise for both research and clinical purposes [6]. However, MRI studies in younger age groups remain less numerous when compared to those of adults, adolescents or infants, which is mainly due to technical and practical difficulties when performing pediatric neuroimaging sessions. The current video-protocol presents hands-on solutions addressing the main practical challenges that may have prevented research groups from performing (f)MRI experiments in young children.

Challenges of pediatric neuroimaging are numerous, but researchers agree that the two main obstacles to overcome are: level of anxiety/distress and participant's movement [2,4,7,25]. Anxiety and distress are commonly reported in clinical patients undergoing imaging procedures. It is estimated that 4 to 20% of all patients refuse to undergo the MRI session or terminate an imaging session before completion [27]. An incomplete clinical imaging session can have serious implications because it may delay proper diagnosis and possible treatment [22]. MRI sessions in children have been reported to impose even higher levels of anxiety/distress [7,18]. However, Rosenberg et al., (1997) could show that distress in children aged 6 to 17 can be significantly reduced by careful subject preparation, including the use of mock scanners.

The intense scanner noise generated by the shifting of gradient coils during conventional continuous image acquisition is one potential cause for anxiety or discomfort [28]. This scanner background noise (SBN) may not only cause anxiety and discomfort in the participant, but can

potentially interfere with experimental paradigms (e.g. during auditory or attention tasks[29,30]. One way to circumvent the exposure to the SBN is to use interleaved data acquisition designs such as the behavior interleaved gradient (BIG) technique [31,32] or sparse temporal sampling [29,30,33-36] (see Gaab et al. 2007 for a detailed discussion on advantages and disadvantages of 'silent' imaging designs).

As an additional obstacle to overcome, movement restriction is necessary to obtain high quality and diagnostically relevant data. In clinical practice, children below a certain age (usually between 6 to 8 years) are often imaged using sedation or general anesthesia (GA) [20]. However, besides possible risks to the child, GA and sedation both lead to increased imaging time and higher costs due to the use of external staff, equipment and medications [23]. Sedation or GA is not used during fMRI due to its potential influence on the blood level dependency contrast (BOLD contrast) [1]. Furthermore, many neuroimaging tasks require the child to be alert and responsive.

It has been shown that play therapy, simulation and behavioral approaches (e.g. cognitive behavioral therapy, behavioral reinforcement) are successful methods to reduce anxiety, reduce overall movement and to allow MRI without sedation in children as young as 3 years of age [23,14]. The current protocol incorporates ideas and elements of the main behavioral management techniques to date into one complete neuroimaging protocol and thereby aims to offer researchers as well as clinicians hands-on guidelines to design and conduct imaging sessions with awake, young children. The use of the current protocol has proven to increase the number of children able to successfully complete a neuroimaging session. The use of a child-friendly and age appropriate pediatric neuroimaging protocol may also allow clinicians to reduce the use of sedation or GA in children undergoing imaging procedures and is expected to increase the emergence of pediatric imaging studies in younger age groups.

4.1.4 DISCLOSURES / ACKNOWLEDGEMENTS

We thank participating children and families, all staff at the Children's Hospital Boston (CHB) with special appreciation to the MRI technicians, without whom our studies could not be conducted. We are especially grateful to Arnold Cyr for participation and help during our video shoot and to operation manager Patricia Devine at the CHB Waltham. Thanks to the research and technical staff at MIT's Athinoula A. Martinos Imaging Center for sharing experience in MR image acquisition and analysis.

This research was funded by the Charles H. Hood Foundation, a Children's Hospital Boston pilot grant and the Swiss National Foundation (N.M.R.)

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4.2 **STUDY 2:** PEDIATRIC NEUROIMAGING IN EARLY CHILDHOOD AND INFANCY: CHALLENGES AND PRACTICAL GUIDELINES

Accepted for Publication in Annals of the New York Academy of Sciences (2011)

SHORT TITLE: Pediatric Neuroimaging in Early Childhood and Infancy

Nora Maria Raschle [1,2]; Jennifer Zuk [1], Silvia Ortiz-Mantilla [3], Danielle Sliva [4], Angela Franceschi [5], P. Ellen Grant[2,4,5,6], April A. Benasich [3], Nadine Gaab [1,2,7]

[1] Laboratories of Cogntive Neuroscience, Children's Hospital Boston, 1 Autum Street, Boston, MA 02115

[2] Harvard Medical School, 25 Shattuck Street Boston, MA 02115, 13 Appian Way
Cambridge, MA 02138-3703

[3] Center for Molecular and Behavioral Neuroscience, Rutgers The State University of New Jersey, 197 University Avenue, 07102, Newark, NJ, USA

[4] Fetal-Neonatal Neuroimaging and Developmental Science Center, Children's Hospital Boston, 1 Autumn Street, Boston, MA 02115

[5] Department of Radiology, Division of Neuroradiology, Children's Hospital Boston

[6] Department of Medicine, Division of Newborn Medicine, Children's Hospital Boston

[7] Harvard Graduate School of Education

Corresponding author:

Nadine Gaab, PhD

Children's Hospital Boston, Department of Medicine, Division of Developmental Medicine

Laboratories of Cognitive Neuroscience
1 Autumn Street, Mailbox # 713
Boston, MA 02115

nadine.gaab@childrens.harvard.edu

www.babymri.org

www.childrenshospital.org/research/gaablab

phone: (857)-218-3021

fax: 617-730-0518

4.2.1 ABSTRACT

There has been an increase in the use of structural and functional magnetic resonance imaging (fMRI) to investigate typical and atypical brain development. However, in contrast to studies in school-aged children and adults, MRI research in young pediatric age groups is less common. Practical as well as technical challenges when imaging infants and children present clinicians and research teams with a unique set of problems. These include procedural difficulties (e.g. participant anxiety or movement restrictions), technical obstacles (e.g. availability of child appropriate equipment or pediatric MR head coils), as well as the challenge of choosing the most appropriate analysis methods for pediatric imaging data. Here we summarize and review pediatric imaging and analyses tools and present neuroimaging protocols for young non-sedated children and infants with guidelines and procedures that have been successfully implemented in research protocols across several research sites.

Key words: pediatric: imaging; children; magnetic resonance imaging; fMRI; MRI

4.2.2 INTRODUCTION

The advent of magnetic resonance imaging (MRI) has opened up new possibilities for studying human brain structure and function across the lifespan. An increase in the use of functional and structural MRI in infants and young children can further add to our understanding of brain development. For example, MRI research has revealed differences in brain structure and function in individuals with disabilities (e.g. dyslexia[1-3]) compared to typical controls, and working with infants and young children may unveil the developmental trajectory of such disabilities. Neuroimaging young children additionally allows for the investigation of brain plasticity during this rapid developmental period, and potentially can reveal how certain perceptual, procedural and cognitive skills, such as music perception and musical skills, develop[4]. However, in contrast to studies in school-aged children and adults, MRI research in young pediatric age groups is less common[5]. Studies involving children under 6 years of age are particularly rare, given the practical and technical challenges involved (e.g.;[5,6]). Practical challenges of pediatric neuroimaging sessions include procedural difficulties (e.g. participant's

anxiety or motivation, movement restriction or motivation, putting an infant to sleep in an unfamiliar environment, parent's anxiety), technical obstacles (e.g. availability of child appropriate equipment, masking and attenuation of scanner background noise, etc.), as well as the challenge of choosing the most appropriate analysis methods (e.g. pediatric brain templates, using adequate movement detection tools). In clinical populations, MRIs of infants and children are routinely obtained under sedation[7-9] which eliminates a subset of these challenges. However, for ethical reasons sedation is not an option for most developmental neuroimaging research. Furthermore, there is a strong push from clinicians and hospital administrators to reduce the overall need for sedation and anesthesia for cost containment and more importantly to prevent any potential negative sequelae, particularly in those receiving multiple MRI studies.

Several methods have been developed in order to improve an infant or child's compliance during neuroimaging sessions within the clinical (e.g.;[10-12]) or research setting (e.g.;[13,14]). General approaches for imaging young children include play therapy[14], behavioral training[10-12,15-17] and simulation[18], the use of mock scanner areas[13,19], basic relaxation[20] and a combination of these techniques[21]. The most common practices for non-sedated newborns and infants are the natural sleep technique[22-25] and the feed and wrap procedure[26,27]. Tables SI1 and SI2 provide a literature overview of published protocols, guidelines and empirical research studies using pediatric neuroimaging protocols and their sample size and success rate.

The current paper summarizes successful methods and aims to provide applied guidelines and recommendations on how to successfully perform neuroimaging studies in non-sedated infants and young children. Furthermore, strategies for overcoming experimental and analysis limitations as well as ethical implications of neuroimaging in pediatric populations are discussed.

4.2.3 GENERAL CONSIDERATIONS

The age of a pediatric participant taking part in neuroimaging research should strongly influence the research protocol for pediatric imaging. Preschool-aged children may participate in structural and functional neuroimaging studies, where the child is required to be awake and alert while performing a certain perceptual or cognitive task. Infants are usually enrolled in studies of brain structure or resting state fMRI which is performed while the participants are asleep. fMRI techniques have been successfully applied in awake infants, but report a very high attrition rate[28,29]. While the focus in working with preschool-aged children or older mostly lies on the child itself, the caregiver-child interaction becomes just as important during infant neuroimaging. Overall, clear communication and a child-centered, age-appropriate approach are fundamental aspects of pediatric neuroimaging.

***Terminology*:** When interacting with participating children and families it is imperative to use positive, child-friendly terminology that can be easily understood. A session may be started with "Do you know what will happen today?". All equipment should be labeled in a child-appropriate way: for instance, the MRI machine may be called "*brain camera*", the scanner noise "camera click" and the head coil "*mirror holder*". Phrases like "It is really loud but won't hurt you" or "Are you doing okay inside the machine?" should be avoided. Furthermore, careful communication with all family members present during the session is as important, if not more important than the communication with the participants themselves to avoid parental/caregiver anxiety which in turn impacts the behavior of the young child or infant. This involves giving the parents a clear outline of the neuroimaging session, describing each step and tool involved, reviewing safety considerations and clarifying the research team's goal. When imaging infants, potential stress may be avoided by telling parents upfront that it is not unusual for a child to fail to fall asleep on the first visit, or to wake up before the protocol is completed. A website describing each protocol step, tool and challenge can help with the preparation process for any age group.

Environment: Scheduling an initial introductory meeting prior to the first neuroimaging session can help diminish both parent and child anxiety by familiarizing them with the research team and setting. Photographs, and/or a brief video overview of an actual session (either via webpages or brochures) may be combined with a tour of the actual MRI area or the mock scanner environment. Research teams working with preschoolers and older children especially benefit from the use of a mock scanner environment prior to or on the day of testing. It enables the research team to demonstrate the actual imaging session and may include a mock scanner with a moveable scanner bed, head coil, response tools, mirror and video system, and integrated MR sounds. Some facilities even incorporate a feedback system as part of the mock scanner area, allowing for the observation of movement and appropriate feedback to train children to lie still (e.g. [10,17]). Most importantly, the mock scanner area provides a child-friendly, appropriate preview of the actual neuroimaging session, and permits the research team to adopt a playful approach to an otherwise strictly medical topic. In addition, research teams are encouraged to have child appropriate toys, child-sized table and chairs, snacks and drinks and to invite participants to bring family and friends to increase children's comfort and motivation. When imaging infants, the mock scanner area is used mainly to familiarize the parents with the scanner equipment and the MRI sounds. Mock preparation further offers an opportunityto develop a relationship between the infant, and the researcher, and can be used to recreate individual napping/bed-time routines within the MRI environment.

Affective State**:** It is crucial to recognize feelings of anxiety, frustration or boredom and address potential issues in a child-friendly manner, since **c**hildren are not always able to express emotions directly. Gauging parent comfort and the level of continued consent throughout the process is equally important, particularly during neuroimaging of infants. The parent's comfort level directly influences the infant's feelings of well-being and contentment, which is critical during the natural sleep technique. Given their expertise in child development and extensive experience with children/families in the hospital environment, a child life specialist (CLS) can be an integral part of the multidisciplinary pediatric neuroimaging team.

MRI Equipment: Depending on the scope of the pediatric neuroimaging session, different MRI compatible tools may be needed. This section highlights some examples of equipment involved during neuroimaging sessions with infants and children.

- *Response Buttons*: Response tools used during the neuroimaging session should be age-appropriate in size and shape. It is recommended to position them comfortably to diminish motion when the participant attempts to reach or play with them (e.g. placing child-friendly buttons an arm-length from the participant works well).

- *Audio System:* The frequency of sounds emitted during MR image acquisition ranges from 0-9,000 Hz[30] at intensity levels up to 115 dB with 3T[30]. When working with young children who are participating in an auditory research experiment, child-friendly ear buds and/or child-sized headphones can mask the majority of scanner background noise while allowing for the presentation of auditory stimuli. When working with infants, the goal is to decrease scanner background noise as much as possible to avoid sleep disruption or startle. The noice can be reduced by 20-30 dB with the use of foam earplugs or industrial-grade earmuffs[31]. In addition, music or the infant's favorite lullabies can be played to mask some of the variations in the scanner noise. A steady-state sound can be an aid to sleep; however, noise that abruptly changes in sound level or intensity in a non-progressive manner is much more likely to result in arousal and waking.

- *Motion Attenuation:* A foam mattress to line the scanner bed reduces the amount and intensity of vibration, additionally increasing comfort. For sleeping infants, a foam helmet can help reduce bone conductance, which adds sound attenuation of about 6 dB, reduces vibration and provides additional stability.

- *Video/Video-Goggle System:* For imaging older children, a video system can be used to present experimental stimuli or movies during image acquisition. However, younger

children may be frightened by a goggle system so a traditional projector- screen combination may be used.

4.2.4 EXPERIMENTAL DESIGN AND IMAGE ACQUISITION

Pediatric imaging for research purposes presents many challenges during both image acquisition and data analysis. Challenges may begin long before the first image is taken, in fact as early as during the conception and design of the research.

Experimental Design: Young children often have difficulties switching between two different task instructions, however, task switching is frequently required during a traditional block or event-related design in fMRI. Our experience has shown that if possible, it is advisable to use a block design and to separate task conditions (e.g. experimental task and control task) into two separate runs to avoid confusion. Furthermore, the overall session length should be as short as is feasible and should not be any longer than 90 minutes for a preschooler (which would include short 5-6 minute runs with breaks between each run and a total of maximal 30-40 minutes of actual scanning). In addition, the intense scanner background noise (SBN), generated by the shifting of gradient coils during conventional continuous image acquisition, is one potential cause of child anxiety or discomfort. SBN affects auditory stimuli delivery[32],leads to activation in auditory/language areas[33,34], leads to differences in attentional demands[35], and also influences the default mode[36]. Inhibiting the SBN during a cognitive demanding task can be quite difficult for a young child and/or a clinical population and this should be taken into account when comparing different age groups or clinical and non-clinical populations. One way to circumvent the exposure to the SBN is to use interleaved data acquisition designs, such as sparse temporal sampling[33,34,37], if time permits.

Image Acquisition: There are many challenges during image acquisition and analysis of pediatric imaging data. These barriers are most prevalent in the first three years of life, but are also present in older children and may include challenges relating to design limitations (e.g. constrained session duration in children, leading to a decrease in statistical power; difficulty

designing task-based fMRI for infants, since MR studies are most successful when the infant is imaged asleep). Challenges may also include the presence of increased movement-related artifacts or differences based on distinct anatomy (e.g. difficulties in obtaining MR head coils that provide similar fit across age, differences in brain shape and size across age, differences in brain contrast, baseline diffusivity, baseline blood flow and regional regulation, the shape of the hemodynamic response function or default mode of brain function across age).

Many research groups are currently working on finding solutions for these challenges. For example, many collaborative groups including ours combine approaches from industry and child life professionals in the hospital setting and further work on optimizing techniques. In parallel, technical groups are developing prospective motion mitigated sequences and MRI coils tailored to the head size of the subject are also under development[38,39]. Development of novel pulse sequences that exploit high density phased array coils to increase the speed of image acquisition have the potential to further increase success. Pediatric brain templates are becoming available to improve data analysis and help account for age-related changes (e.g.,[8,40,41]). Further, several research labs have developed techniques to better align and normalize brains which differ in size and shape. For instance, it has been shown that surface-based registration can provide significantly better alignment across different age groups [42]. However, these templates do not allow capture of the full range of information available and therefore multiple sites are working on "4D" atlases that provide information on maturation of substructures [43].

Overall, there is still much that is unknown about the biological differences between the immature and mature brain that could influence data analysis. At each step along the way, the fundamental assumptions for any data analysis tool need to be questioned to be sure these assumptions still hold hold for the age of infant or child participant. As a result, a close collaboration between technical and developmental experts is needed as we continue to study these younger age groups.

4.2.5 PREPARATION AND NEUROIMAGING PROCEDURES FOR INFANTS AND CHILDREN

Neuroimaging Infants: Obtaining detailed information about the child's nap and feeding schedule is helpful in facilitating the preparation for an infant session and for deciding the best time to schedule the MRI. For some babies, and always in accordance with the parents' wishes, an earlier nap may be omitted so that the infant is sleepy upon arrival. Completing several interesting but not too stimulating tasks, immediately prior to the scan, can further fatigue the child. Parents are encouraged to bring anything that the infant may need for her/his bedtime routine (a familiar blanket, favorite toy or lullaby music). Listening to a CD containing scanner background sounds (optionally overlaid with favorite lullabies) prior to the day of the neuroimaging session will prepare the infant for the upcoming procedure. Exposure to the scanner sounds should ideally be started at least a week prior to imaging. Encouraging frequent exposure to the sounds (e.g. during both awake and nap times) increases the habituation effect and may decrease startle responses during neuroimaging.

When scanning infants, replicating normal bedtime routines in the imaging suite, including bathing, feeding, dimming the lights and playing soft lullaby music, has proven to be effective[22]. Offering a rocking chair, portacrib, bathtub, or blankets for swaddling may help parents to put the baby to sleep. Playing a CD of the MRI sequences in the room where the infant falls asleep provides a stable auditory environment throughout the process. In order to ease the transition between a nursery-type environment and the MRI suite, an alternative approach is to have the infant fall asleep inside the MRI suite using a MRI compatible (inflatable) crib. Some caregivers may decide to perform their sleep routine (e.g.; nursing, lullabies etc.) inside the MRI suite or even on the MRI scanner bed. The caregiver should be allowed to try to put their child to sleep, as long as they are comfortable. The research team should leave them on their own if at all possible and not "hover". Reserving at least a two-hour time slot with the MRI allows for flexibility.

Once the infant has fallen asleep, earplugs, earmuffs ("Minimuffs," Natus Medical Inc., San Carlos CA) and a sound attenuation helmet can be placed on the infant[24,25] . Earplugs should be

placed after feeding as having the ears blocked while nursing can make infants uncomfortable. The infant can be slowly and gently lied on the prepared scanner bed, which should be ideally covered with a well-secured visco-elastic foam mattress. Laying a warm blanket on top of the mattress can alleviate the cool temperature in the MRI suite. The infant's head should then be positioned into the coil and the researcher can then carefully adjust the restraint straps in place to secure the infant and limit his/her movements. Once the infant has been snuggled into the space with a soft blanket and sleeps soundly, the scan can proceed.

Throughout the scan, the caregiver and a team member should stay in the imaging suite. If the infant begins to wake, MRI acquisition can be paused and an attempt made to soothe the infant back to sleep. If the infant cries or becomes distressed at any time during the scan, it is advisable to stop and immediately remove the baby from the scanner. Regardless of successful or failure of image acquisition, offering toys and onesies to infants are a nice token of appreciation and after a success, providing a CD with images of the infant brain to take home is an incentive for parents.

Neuroimaging Young Children *(see also Raschle et al., 2009)***:** Presenting young children with a cognitive task to complete during functional imaging requires the adaptation of the tasks, instructions and incentives used. A child-friendly theme can be useful in guiding a young child through the training and actual neuroimaging session. For example, an adventure story can motivate the child to finish all of the tasks requested. Short movies can be useful to lead into the session, engage the child, and reduce any initial anxiety. Additionally, virtual sticker charts can be used to provide feedback about the progress of the neuroimaging session and to motivate the child to complete as many sequences as possible.

Children 4 years and older are best prepared for the (f)MRI session in a mock-scanner area. The scope of the neuroimaging session can be explained to participants and families using applied examples and the material used during actual imaging (e.g.; button boxes, headphones) can be revisited in a safe way. Once a general introduction to the MRI has been provided, the child can listen to instructions for the task and then practice while sitting on the mock scanner bed. After

the child understands the task, the researcher can gradually add the use of headphones, presentation of pre-recorded scanner sounds in the background, and lying down in the mock scanner bed while simultaneously practicing the training task to replicate the actual MRI experience. If the child cannot distinguish between left and right, a response button may be labeled “monkey button” instead of “right button” and a toy animal can be placed on the appropriate side as a reminder.

One major challenge of working with young children during functional tasks is keeping movements to a minimum during image acquisition. It is advisable to discuss the impact of motion on the brain images with the child. A digital camera may be used to demonstrate the impact of movement on image quality. Print-outs of sharp and blurry pictures (e.g. of animals) or playing games, such as the game of “freeze” (challenge the child to stay still as long as possible), can be used for illustration purposes. It is best to remind the child not to speak during image acquisition, since this can cause reduced task performance and data quality. An additional helpful strategy is to train the child that a gentle hand press on their leg indicates there is too much movement. A member of the research team shouldstay in the MRI room throughout the session with the child and should implement the “hand on leg” procedure if the child demonstrates significant movement, which serves as a means of communication between the research team and the child during the experiment.

If a mock scanner is not available, game strategies such as employing play therapy techniques[44] are a recommended alternative. Providing pictures or videos of an MR scanner effectively depicts the MRI experience[10], and desensitization to the procedure by this exposure and operant training techniques help to reduce anxiety in children[12,17].

Researchers should keep in mind that the transition from mock training to the actual MR also brings changes to the environment (less toys, more medical personnel and supplies, change in temperature, etc). Thus, it is important to be attentive to the child’s reaction upon entering the room and respond accordingly. Allowing the parent to accompany the child and offering comfort items may effectively smooth the transition. If a child displays resistance to any aspect

of the MRI experiment, address the concerns immediately and carefully. Offering breaks during the neuroimaging session can be helpful. The researcher should take all the time necessary to make the child comfortable with the MR environment. Upon completion of image acquisition, offering incentives and a CD with images of the brain to the child is a nice reward for participation.

4.2.6 ETHICAL IMPLICATION AND CONCLUSION

Here we provide applied guidelines and recommendations on how to successfully perform neuroimaging studies in non-sedated infants and young children. These techniques have been proven to be successful in a large group of infants and young children across several research sites (see SI3). It is important to keep in mind that along with the advent of more accessible (pediatric) neuroimaging, ethical challenges have also arisen. While these issues have emerged and have been discussed in detail in regard to adult neuroimaging, such ethical issues are not only present when considering pediatric neuroimaging, but may even be magnified[45,46]. However, the anticipated benefits of using pediatric fMRI in non-clinical populations are considerable and may have far reaching advantages including application to classroom settings[46]. Nevertheless, researchers should carefully consider what method is most appropriate for their experimental question and participant age range. Thomason (2009) has highlighted the positive experiences of pediatric research participants,but such data is not available yet for younger children[47]. Furthermore, Connors & Singh (2009) strongly emphasize that neuroimaging data is often misinterpreted by the general public and that there are a series of subtle ways in which neuroimaging data is and will affect children's lifes such as the shaping of national health, strategies for criminal risk assessment and educational practice and its overall implication for policy, education and family life[48].It is also important to keep ethical considerations in mind and to frequently re-evaulate advances in the field of pediatric imaging in terms of their ethical implications. This will help improve existing imaging protocols and guidelines and will also facilitate development of new technological advances that will improve comfort for the children scanned as well as enhancing data quality.

4.2.7 ACKNOWLEDGMENTS

Thank you to W. C. Liu and to D. Johnson from UMDNJ for invaluable help in running non-sedated scans in infants. Thanks as well to the researchers and staff at the Center for Molecular & Behavioral Neuroscience who spent many hours designing the infant protocol and patiently acquiring scans. In particular thank you to J. Flax, S. Paterson, N. Badridze, J. Byrne and S. Marken. We also would like to thank the Children's Hospital Boston MRI Team and the members of the Gaab lab who helped conducting these scans. And of course, thank you to all the parents, babies and children who worked so hard to help us acquiring these important images of developing brain.

This work was supported by a grant from the Harvard Catalyst (to NG and EG), the Santa Fe Institute Consortium (to AAB) with additional funding from the Elizabeth H. Solomon Center for Neurodevelopmental Research.

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Aim2: *To test whether the neuronal correlates of phonological processing differ between children with or without a family history of DD prior to reading onset and to investigate whether there are any relations to standardized behavioral measurements*

4.3 **STUDY 3:** FUNCTIONAL CHARACTERISTICS OF DEVELOPMENTAL DYSLEXIA IN LEFT-HEMISPHERIC POSTERIOR BRAIN REGIONS PREDATE READING ONSET

N.M. Raschle, J. Zuk, N. Gaab

Accepted for publication in PNAS (2011)

4.3.1 ABSTRACT

Individuals with developmental dyslexia (DD) show a disruption in posterior left-hemispheric neural networks during phonological processing. Additionally, compensatory mechanisms in children and adults with DD have been located within frontal brain areas. However, it remains unclear when and how differences in posterior left-hemispheric networks manifest and whether compensatory mechanisms have already started to develop in the pre-reading brain. Here we investigate functional networks during phonological processing in 36 pre-reading children with a familial risk for DD (n=18, average age= 66.50 months) compared to age and IQ matched controls (n=18; average age=65.61 months). Functional neuroimaging results reveal reduced activation in pre-reading children with a family-history of DD (FHD+), compared to those without (FHD-), in bilateral occipitotemporal and left temporoparietal brain regions. This finding corresponds to previously identified hypoactivations in left hemispheric posterior brain regions for school-aged children and adults with a diagnosis of DD. Furthermore, left occipitotemporal and temporoparietal brain activity correlates positively with pre-reading skills in both groups. Our results suggest that differences in neural correlates of phonological processing in individuals with DD are not a result of reading failure, but are present before literacy acquisition starts. Additionally, no hyperactivation in frontal brain regions was observed, suggesting that compensatory mechanisms for reading failure are not yet present.

Future longitudinal studies are needed to determine whether the identified differences may serve as neural pre-markers for the early identification of children at risk for DD.

4.3.2 INTRODUCTION

Developmental dyslexia (DD) is a specific learning disability that affects about 5-17% of all children (2-3), characterized by difficulties with accurate and/or fluent word recognition, and poor spelling and decoding performance. DD cannot be accounted for by poor vision, hearing or a lack of motivation. Molecular-genetic, twin and family studies have shown a marked familial risk for DD, with an increasing prevalence in families with one or more members with a diagnosis of DD or reading difficulties (e.g. (5, 6)). In addition, several DD susceptibility genes crucial for early brain development have been reported (7-10). DD can have severe social and psychological consequences (11-13) and may impact a child's life beyond their academic pursuits. Studies have shown that children with learning disabilities are less likely to complete high school (14) and are more likely to enter the juvenile justice system (15).

Most researchers, clinicians and reading specialists agree that DD typically results from a weakness in the ability to manipulate oral speech sounds of language (3, 16). Individuals with DD are often unable to access the underlying sound structures of words, creating a difficulty in mapping sounds to written language (17-20). Phonological processing skills have been found to be a key predictor of later reading ability in preschool and elementary school-age children (21-23; 24-33). In addition to phonological processing deficits, a range of other linguistic impairments have been observed in infants and pre-reading children who later exhibit weak reading scores, including speech perception (25, 28), syntax production and comprehension (34-37), language comprehension (28), receptive vocabulary (24, 36) and rapid automatized naming abilities (25, 36, 38; 39-41).

With the advent of modern neuroimaging tools, it is now possible to study the neural substrates of reading and reading-related processes in the conscious human brain. Functional magnetic resonance imaging (fMRI) studies have revealed a characteristic network of posterior

brain areas typically involved in reading and reading related tasks in children and adults including: (**I**) the dorsal or temporoparietal circuit (including lateral extrastriate and left inferior occipital areas) and (**II**) the ventral or occipitotemporal circuit (including angular and supramarginal gyrus, inferior parietal lobe and posterior aspects of the superior temporal gyrus (45-49)). Cross-sectional studies have demonstrated changes in these highly integrated reading networks depending on reading skill level (e.g. (50, 51)) and converging evidence points toward a characteristic hypoactivation of temporoparietal as well as occipitotemporal brain areas in individuals with DD (50, 52-57, 58-61).

These functional characteristics in posterior brain regions in children and adults with DD have been complemented by anatomical abnormalities. Voxel-based morphometry reveals differences in gray matter volume indices in individuals with DD (when compared to typical reading controls) in various areas of the brain, including left occipitotemporal and temporoparietal areas (50, 67-72), bilateral fusiform (70) and lingual gyrus (69) as well as the cerebellum (67-69). Morphological abnormalities in these regions can be identified even before reading skills are present in children as young as five to six years of age, suggesting atypical early development or even a genetic basis for DD (73).

Furthermore, an increase in activation in left frontal and/or right lateralized anterior brain areas has been shown in individuals with DD (50, 51, 55, 56, 64). This hyperactivation seen in individuals with DD has been suggested to reflect a compensatory mechanism for the dysfunctional reading system (e.g. (44, 50, 56)). Further, it has been shown that right prefrontal activation in children with a diagnosis of DD can significantly predict reading gains 2.5 years later, indicating that these compensatory mechanisms can function as part of the reading network (44).

Although there is converging evidence suggesting a characteristic structural and functional phenotype of DD, the mechanism by which reading networks fail to develop is poorly understood. It remains unclear whether the characteristic hypoactivation within posterior brain regions is present prior to reading onset or whether these develop after reading onset and may

therefore be a result of reading failure. Moreover, it remains unclear whether compensatory mechanisms in anterior brain regions are a unique characteristic of children with DD that predates reading instruction, or whether these form during literacy acquisition. Cross-sectional and longitudinal electroencephalography studies have reported altered neural correlates in infants and pre-schoolers with a familial risk for DD during speech perception and some of these brain measures later predicted reading outcome in elementary school (42, 96-97). These studies strongly suggest that components of deficient reading network may be observed prior to reading onset.

To further examine the emergence of reported abnormal brain activations and characteristic behavioral differences in children and adults with a diagnosis of DD, the present study employed fMRI in pre-school children with (FHD+) and without (FHD-) a familial risk for DD. We hypothesized left-hemispheric hypoactivation in posterior brain regions in children with a familial risk of DD as compared to age-matched controls prior to reading onset. Further, we hypothesized that no differences in anterior brain regions would be seen since we expected compensatory brain regions to form only after repeated reading failure.

4.3.3 RESULTS

Demographics and Behavioral Group Characteristic. Demographics and behavioral group characteristics are listed in **Table S1**. FHD+ children scored significantly lower than FHD- children in standardized assessments of core language Core Language ($t_{(34)}$ =-2.045; p=0.049)), expressive language skills (Clinical Evaluation of Language Fundamentals (CELF) Expressive Language ($t_{(34)}$ =-3.037; p=0.005); VATT Repetition ($t_{(30)}$ =-2.412; p=0.022)), language structure (CELF Language structure ($t_{(34)}$ =-2.195; p=0.035)), phonological processing (Comprehensive Test of Phonological Processing (CTOPP) Elision ($t_{(33)}$ =-2.422; p=0.021) and rapid automatized naming (Rapid Automatized Naming Test (RAN) objects ($t_{(33)}$ =-3.420; p=0.002) and colors ($t_{(33)}$ =-2.586; p=0.014)).

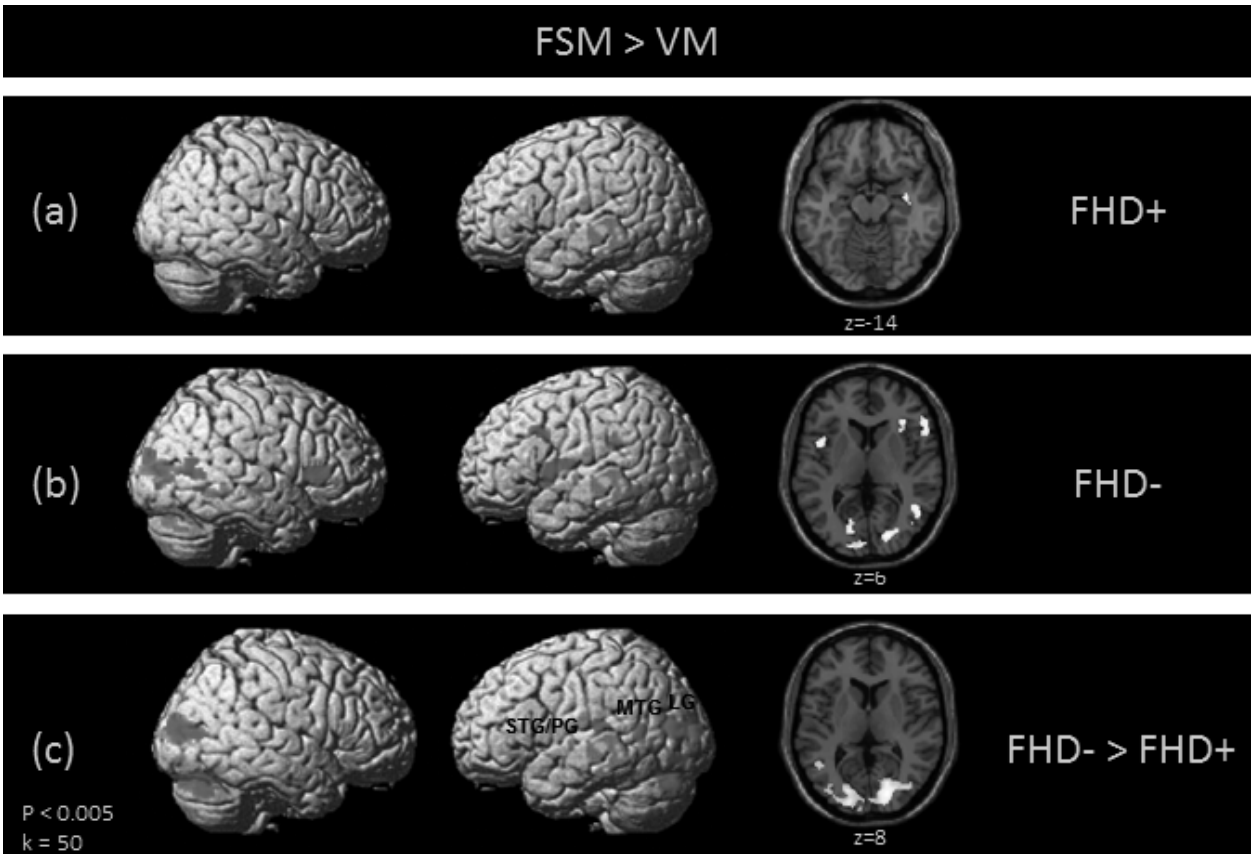

Figure 1. Statistical parametric maps showing brain activation during phonological processing (FSM>VM) for children with (a) and without (b) a family history of DD, as well as group differences between children with compared to without (FHD->FHD+) a family history of DD (c). FHD- show significantly greater activation when compared to FHD+ children in bilateral occipitotemporal and left temporoparietal brain regions as well as left and right cerebellar regions.

fMRI results. Children were asked to listen to two words and decide whether the target words started with the same initial sound (First Sound Matching, FSM). This was contrasted with a Voice Matching Task (VM) in which children listened to the same word pairs but had to decide whether they were spoken by the same voice (See method section for a detailed task description). Whole-brain analysis revealed increased activation for FSM > VM in FHD- children in a number of brain regions, including left fusiform gyrus, left inferior frontal/precentral gyrus, bilateral cuneus/middle occipital, left middle frontal gyrus and right cerebellum (**Figure 1a**). FHD+ children activated the right middle temporal gyrus and right cerebellum for the same

contrast, but failed to show activation in left hemispheric brain regions associated with phonological processing and reading (**Figure 1b**). An independent 2-sample t-test was employed to examine differences in brain activation during FSM vs. VM between the two groups of children. This analysis revealed significantly greater activation for FHD- compared to FHD+ children in bilateral occipitotemporal (left lingual gyrus and bilateral middle temporal/occipitotemporal gyrus), left temporoparietal (left superior temporal/postcentral and middle temporal gyrus) brain regions as well as left and right cerebellum. (**Figure 1c and Table 1**). The opposite contrast (FHD+ > FHD-) did not yield any significant voxels. Regions of interest analyses, derived from the FSM>VM group comparison, were used to compute correlational analysis with behavioral measures of pre-reading skills. These results demonstrate a positive correlation of phonological processing skills (CTOPP non-word repetition) with brain activation in left lingual gyrus (LG; p=0.003) and superior temporal/precentral gyrus (STG/PG; p=0.013) in FHD- children; but no significant correlation was found for left middle temporal gyrus (MTG) and phonological processing (p>0.05). In FHD+ children, brain activity within the LG (p=0.016), MTG (p=0.003) and STG/PG (p=0.018) all showed a significant positive correlation with phonological processing. Bar graphs illustrate the amount of brain activity in FHD+ and FHD- children within the three regions of interest (LG, MTG, ST/PG) during phonological processing (FSM>VM; **Figure 2**). FHD+ children predominantly show negative parameter estimates for phonological processing (first sound matching compared to voice matching) in these regions of interest.

Table 1. Significant differences in brain activation between children with (FHD+) and children without (FHD-) a family history of dyslexia during phonological processing (FSM>VM; FHD->FHD+; at p<0.005 uc; k=50).

Region	Coordinates X	Y	Z	Z score	Size, voxels
Occipitotemporal Lobe					
Middle Temporal/Occipitotemporal Gyrus (R/L)	18	-84	8	4.44	1142
Lingual Gyrus (L)	-16	-86	-10	3.63	84
Temporoparietal Lobe					
Superior Temporal/Postcentral Gyrus (L)	-60	-28	14	3.19	50
Middle Temporal Gyrus (L)	-48	-56	6	2.91	83
Other					
Cerebellum/Fusiform Gyrus (L)	-28	-76	-28	3.75	206
Cerebellum (R)	16	-62	-18	3.86	360
Cerebellum (R)	44	-70	-32	3.42	93

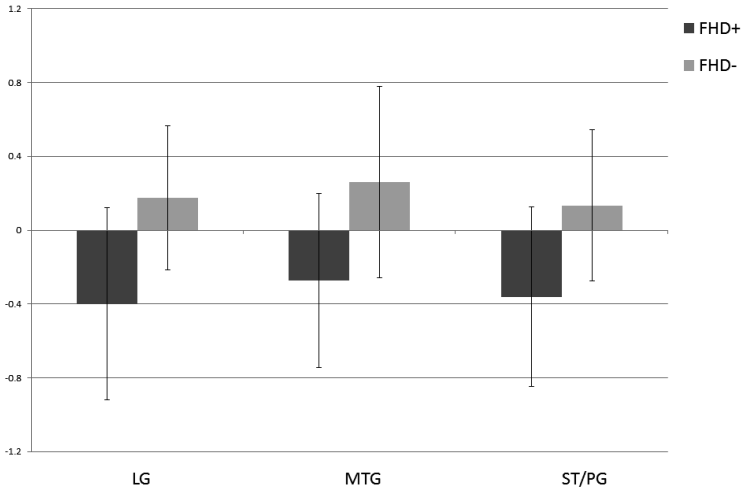

Figure 2. Mean brain activation (weighted parameter estimates) during phonological processing (FSM>VM) in left lingual gyrus (LG), middle temporal gyrus (MTG) and superior temporal/postcentral gyrus for children with (FHD+) and without (FHD-) a family history of DD. FHD+ children predominantly show negative parameter estimates, whereas FHD- children predominantly show positive parameter estimates for phonological processing (first sound matching > voice matching) in these regions of interest. Error bars represent standard deviations.

In-Scanner Performance. Due to a technical problem, the behavioral responses for the experimental and control tasks could not be recorded in one child and no data for the control task could be recorded for another child. Both children (FHD-) were still included in the analysis as their performance during the training session indicated that the tasks were well understood. In-scanner performance revealed that FHD+ children scored significantly lower than FHD- children during phonological processing (FSM; FHD+/FHD-: 13.83/21.06; $t_{(33)}$ =-4.77; p=0.000), but no difference was found during VM (FHD+/FHD-: 19.39/20.56; $t_{(32)}$ =-0.47; p=0.641). FHD+ children responded faster during VM (FHD+/FHD-: 1970ms/2279ms; $t_{(32)}$ =-2.26; p=0.031), but not FSM (FHD+/FHD-: 2040ms/2262ms; $t_{(33)}$ =-1.324; p=0.194) when compared to FHD- children.

4.3.4 DISCUSSION

The current study provides neuroimaging evidence for the disruption of left hemispheric posterior neural networks during phonological processing in preliterate children with a familial risk for DD. Consistent with previous neuroimaging studies in older children and adults with a diagnosis of DD, pre-reading children with a familial risk for DD (FHD+) already show reduced activation within a left hemispheric network including occipitotemporal (lingual gyrus) and temporoparietal brain areas (superior temporal/postcentral and middle temporal gyrus) compared to typical controls (FHD-).

Moreover, brain activity within the left lingual as well as the superior temporal/postcentral gyrus positively correlates with phonological processing skills in children with and without a family-history of DD. FHD+ children also demonstrate a positive correlation between activation in middle temporal gyrus and phonological processing. In addition to the altered neural correlates, FHD+ children score significantly lower on standardized tests of phonological processing, expressive language skills and rapid automatized naming. Since all children were pre-literate at the time of testing, the present findings cannot be attributed to reading failure within the at-risk subgroup. Additionally, no differences in home literacy environment or socioeconomic status were observed. Thus, our results suggest that these behavioral and neural differences in children at risk for DD must reflect a mechanism that develops within the first few years of life or may even have a biological origin. However, it is important to note that most children came from households of relatively high socioeconomic status (SES) and also demonstrated relatively strong language skills overall. Future research is needed to determine whether the observed differences can also be found in children from lower SES households and those with poorer language scores.

Converging evidence from many neuroimaging studies points toward a characteristic hypoactivation of left-hemispheric temporoparietal (50, 52, 54-57) and occipitotemporal (50, 52-54, 56) brain regions in children and adults with DD when compared to typical reading controls. Furthermore, reduced gray matter volume indices in temporoparietal and

occipitotemporal brain regions have been reported in pre-reading children at risk for DD compared to their peers (73). The left temporoparietal region of the brain is known to be crucial for the integration of letter and speech sounds (77) and has consistently demonstrated activation during phonological processing tasks in typically reading children and adults (for reviews see (46-48)). In individuals with DD, a hypoactivation of the left temporoparietal region of the brain seems to reflect an inability to map the sounds of languages (phonemes) to its written counterparts (letters/graphemes; 50, 52-57). The left hemispheric occipitotemporal region seems to be involved in the processing of words and/or pseudowords in typical reading children and adults (for reviews see (46-48)) and has been called the 'visual word form area' (78). Several studies suggest that within this region, letters are represented and processed independently of the perceptual dimension of stimulus presentation (78-80). Furthermore, it has been shown that the initial development of visual tuning for print within inferior occipitaltemporal brain regions is delayed in children with DD (81).

In the present study, we found the same characteristic functional atypicality within temporoparietal (superior temporal/postcentral and middle temporal gyrus) and occipitotemporal brain areas (left lingual) during phonological processing when comparing pre-reading children with a familial risk for DD to those without such a history. It has been hypothesized that hypoactivation in DD within left temporoparietal and occipitotemporal areas of the brain are fundamental to the language disorder itself, as differences in these areas during reading tasks are apparent even when comparing children with DD to younger, typical readers, who are on the same reading level (50). Our results support this hypothesis and one can further hypothesize that pre-reading children at risk for DD exhibit reduced gray matter volume indices in left temporoparietal and occipitotemporal brain regions (73) which then lead to a disruption of the network typically involved in phonological processing and subsequent reading failure.

Our results further show a positive correlation between phonological processing abilities and brain activation in left lingual gyrus as well as superior temporal/postcentral gyrus for children

with and without a familial risk for DD. This finding underlines the importance of these posterior brain regions for phonological processing abilities in the pre-literate brain. Only children with a familial risk for DD show additional correlations between phonological processing skills and brain activity in left middle temporal gyrus. Therefore, we hypothesize that phonological processing within dorsal and ventral reading networks develop differently for FHD+ and FHD- children. For all children a specialization in left lingual and superior temporal/postcentral gyrus is emerging, visible by a higher skill level of those children with more brain activation in these areas (positive correlation of phonological processing skills and brain activity in left lingual and superior temporal/postcentral gyrus). However, most of the children at risk for DD show negative weighted parameter estimates in left lingual and superior temporal/postcentral gyrus suggesting less specialization than the children with no risk, which show predominately positive weighted parameter estimates in these regions. On the contrary, in left middle temporal gyrus children with no risk do show positive weighted parameter estimates but no correlation with phonological skills suggesting that this region has been fully developed and increased skill level does not lead to an increase in activation in this region. In children at risk for DD, mostly negative weighted parameter estimates are observed in middle temporal gyrus, which again suggests less specialization than the children with no risk (predominately positive weighted parameter estimates in these regions). However, children at risk show a positive correlation with phonological skills in this region indicating an emerging specialization depending on the child's skill level.

Our findings are in line with previous research showing that more temporoparietal brain areas are predominantly activated during early reading development, whilst the more occipitotemporal areas specialize later (82). To summarize, we suggest that a specialization for (auditory) phonological processing within dorsal and ventral brain regions takes place in the pre-reading brain. However, specialization in dorsal components of the reading network seems to be delayed in children with a higher risk for DD that impacts their phonological processing abilities. Further longitudinal studies are needed to determine how phonological processing develops in these children.

In addition to the characteristic hypoactivation in individuals with DD, some studies have reported hyperactivity primarily in left frontal and / or right hemispheric regions of the brain in children and adults with DD during reading related tasks (50, 55, 56, 64). In the current study, however, hyperactivation was not observed in children with a familial risk for DD. But it has been argued that hyperactivations in DD reflect compensatory strategies to correct for the dysfunction within the left hemispheric reading network (e.g. (44, 50, 56)) and therefore are most likely develop *after* reading acquisition/failure. Our result supports this hypothesis since no compensatory mechanisms were observed in our pre-reading children. This view is in line with a recent meta-analysis of reading and reading-related tasks in children (mean age 9-11 years) and adults (mean age 18-30 years) with DD, which reported a noticeably smaller number of overactivation foci in pediatric as compared to adult neuroimaging studies (61). It has been hypothesized that this may reflect an increase in reliance on compensatory mechanisms with age or the presence of more variable compensatory mechanisms in children (61).

DD can have severe psychological and social consequences, potentially negatively impacting a child's life. Negative personal experiences and continued unhappiness about failing in school may lead to frustration, aggression, impulsivity and anti-social behavior in some children (11, 83). Identifying children at risk for DD at an early age is crucial and offers the chance to eliminate significant personal and social costs. Identifying a learning disability around mid-elementary school is oftentimes too late, as the delayed development may have already affected a child's vocabulary skills (84) and motivation to read (85). Early identification of reading disability offers a chance to implement early remediation programs, which may lead to a normalization of dysfunctional brain patterns, ideally before compensatory mechanisms are needed.

Future research using longitudinal designs is needed to shed light on the development of this neural network in pre-reading children throughout the development of reading skills. It remains to be determined which of the pre-reading children with a family-risk for DD will develop a

reading disability. Ultimately, the goal will be to determine whether functional differences in pre-reading children can be utilized to predict later reading outcome, and perhaps identify DD.

4.3.5 CONCLUSION

Converging studies illustrate characteristic differences in brain structure and function of children and adults with DD. In the present study, we demonstrate that previously described patterns of hypoactivation in parietotemporal and occipitotemporal brain areas during phonological processing in individuals with DD already exist in pre-reading children with a familial risk for DD. This discovery suggests that functional and structural brain alterations are fundamental to DD and cannot be due solely to reading failure itself. However, future studies are needed to address the question of whether phonological deficits, alterations in the brain's reading network and later reading failure interact with each other in a feedback loop. Furthermore, no compensatory mechanisms in frontal/right hemispheric brain regions were observed in the present sample of preliterate children, suggesting such differences may arise with later reading failure. An advance in the understanding of brain processes in children at-risk for DD may lead to strategies that will reduce the severity of DD after reading onset. Most importantly, this research may reduce the clinical, psychological and social impact of DD.

4.3.6 METHODS

Participants. Thirty six healthy, native English speaking children with (FHD+/n=18) and without a familial risk for DD (FHD-/n=18), have been included in the present analyses. All children are enrolled in the Boston Longitudinal Dyslexia study. 32 children were right handed, whereas for 4 children handedness could not be indicated yet (these children have been labeled as ambidextrous; 3FHD+/1FHD-). FHD+ children (mean age during imaging session 68.44 months) had at least one first degree relative with a clinical diagnosis ofDD; FHD- children (mean age during imaging session 66.72 months) had no first degree relatives with DD or reading difficulties. Children with a family history of reading difficulties, but no clinical diagnosis of DD, were excluded from the study. Furthermore, all children were physically healthy and had no

history of any neurological or psychological disorder, head injuries or poor vision and hearing. The two groups were matched for age, gender and non-verbal IQ (*Kaufman AS & Kaufman NL (1997) KBIT-2: Kaufman Brief Intelligence Test. 2nd ed. 1997, Minneapolis, MN: NCS Pearson, Inc.);* **Table S1**).

All children were screened for pre-reading status (for description see **Text S1**). All participating children were tested between May and November of their kindergarten entry year. This study was approved by the local ethics committee (Children's Hospital Boston). Verbal assent and informed consent was obtained from each child and guardian, respectively.

***Behavioral Group Characteristics*.** Participants were characterized with a test battery of standardized assessments examining language and pre-reading skills such as expressive and receptive vocabulary (Clinical Evaluation of Language Fundamentals, phonological processing and rapid automatized naming (**Table S1).** Additionally, all participating families completed a socioeconomic background questionnaire (adapted from the MacArthur Research Network: http://www.macses.ucsf.edu/Default.htm; for a complete overview of SES questions see **Table S2**) and a home literacy questionnaire (based on (92) as cited in (93); **Table S3**). Both groups were matched for age (age at psychometric testing, p=0.570; age at imaging testing, p=0.264) verbal and non-verbal IQ (KBIT verbal IQ, p=0.739; non-verbal IQ p=0.389) and socioeconomic status (e.g. parental education and total family income over the past 12 month, p>0.05). The behavioral assessment was performed on a different day than the imaging session but the sessions were no more than 6 months apart (average for FHD+ 1.94 months; average for FHD- 1.44 months).

fMRI – Task Procedure (for a more detailed description including stimulus properties see* Text S1*). During the experimental run, children performed a phonological processing task which involved listening to two sequentially presented common object words spoken in a female or male voice Pictures of the objects were presented at the screen simultaneously. Children were asked to indicate via button-press whether the two words presented started with the same first sound or not. This task was contrasted with a rest condition. During the rest condition, children

were asked to look at a fixation cross for the duration of the block. The control task also involved listening to two common object words spoken in a female or male voice. Mirroring the experimental task, pictures that illustrated the spoken words were presented on the screen simultaneously. Participants were asked to indicate by button-press whether or not the gender of the voice matched for the two words presented. This task was also contrasted with a rest condition.

fMRI - Analysis. Acquisition parameters are specified in Text S1. Image processing and analyses were carried out using SPM5 (www.fil.ion.ucl.ac.uk/spm) executed in MATLAB (Mathworks, Natick, MA). Prior to statistical analysis, all images were pre-processed utilizing realignment, normalization and smoothing modules in SPM5. Due to the age of participants, a rigorous procedure for artifact detection was chosen. Upon visual inspection of all raw images, preprocessed images were used to create an explicit mask excluding potential artifactual time points through the art-imaging toolbox (http://cibsr.stanford.edu/tools/ArtRepair/ArtRepair.htm) for each child. In addition, movement regressors were added. Artifactual time points and movement regressors were identified using a movement threshold of 3mm and a rotation threshold of 0.05mm. The resulting images were visually inspected and only those images containing artifacts were discarded for further analysis. Subjects were only included in the analysis when more than 80% of the pictures were artifact free and therefore included in further analysis. The general linear approach implemented in SPM5 was used to analyze the data in a block design for each subject. Contrast images for experimental > control condition ('First Sound matching > Voice matching') were obtained. Contrasts comparing with the rest condition were not computed. Finally, a second-level analysis using a two sample t-test was performed in order to examine functional differences between children with and without a family history of DD. Results are reported at a significance level of $p<0.005$, uncorrected, and extent threshold (ET) of 50 voxels for each group separately and for those regions that showed significantly more activation in FHD- compared to FHD+ children.

Previous research has shown an involvement of left hemispheric brain regions including occipitotemporal and temporoparietal areas during reading and reading related tasks in typical reading individuals (e.g. (46-48)). These regions have shown to be hypoactivated in children and adults with a diagnosis of dyslexia (50, 52-57, 66). Therefore, we chose to investigate the following left-hemispheric regions of interest: left lingual (LG), superior temporal/postcentral (STG/PG) and middle temporal gyrus (MTG). Regions of interest were extracted from the second level T-contrast (FSM>VM) using MARSBAR (94). Correlation analysis within each group separately (FHD+/FHD- children) was used to relate brain function in these regions of interest with phonological processing skills (CTOPP, Non-Word Repetition) using SPSS software package, version 19.0 (SPSS Inc. (1999) SPSS Base 10.0 for Windows User's Guide. SPSS Inc., Chicago IL.). FDR corrected results with a p value below 0.05 are reported as significant.

In-Scanner Performance. Button presses were recorded during the experimental and control tasks. The participants' in-scanner performance was closely monitored (for details see (95)). To ensure that the participants were engaged in the tasks, participants with more than 40% of trials unanswered were excluded from the imaging analyses. Children were instructed to indicate their answer as soon as they saw a question mark appear on the screen (after the presentation of the second word; for task design and figure see **Text S1** and **Figure S1)**. Children were allowed to correct their response. During the training session, the research team provided verbal feedback on trial performance; no feedback was given during actual neuroimaging. Response correction was taken into account in consequent analysis, if it occurred before the first word of the consequent trial was presented. Task accuracy and reaction time were compared between children with and without a family history of DD using paired two-sample T-tests implemented by the SPSS software package, version 19.0 (SPSS Inc. (1999) SPSS Base 10.0 for Windows User's Guide. SPSS Inc., Chicago IL.). Results (sig. 2-tailed) with a p-value less than 0.05 are reported as significant.

4.3.7 ACKNOWLEDGMENTS/FUNDING SOURCES

We thank all participating families. This research was funded by the Charles H. Hood Foundation, a Children's Hospital Boston pilot grant, the Swiss National Foundation, NICHD (RO1 HD65762-01) and the Janggen-Pöhn Stiftung (N.M.R.).

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Supplementary material is available in the appendix.

Aim3: *To test whether the neuronal correlates of rapid auditory processing differ between children with or without a family history of DD prior to reading onset and to examine whether there are any relations to standardized behavioral measurements*

4.4 **STUDY 4:** DISRUPTED NEURAL NETWORKS DURING RAPID AUDITORY PROCESSING IN PRE-READING CHILDREN AT RISK FOR DYSLEXIA

Paper in preparation.

Disruptive neural response during rapid auditory processing in pre-readers at risk for dyslexia - an fMRI study

Raschle, N.M., Stering, P.L. & Gaab, N. *(2010). Oral presentation for the Annual Meeting of the Society for Developmental and Behavioral Pediatrics, Boston, MA; September, 2010.*

Purpose: Developmental dyslexia (DD) is a specific learning disability characterized by difficulties with accurate and/or fluent word recognition, and poor spelling and decoding. Familial occurrences support a genetic basis for DD. The earliest predictors of future reading success include speech processing in infancy; event-related brain potentials during rapid auditory processing, and phonological skills. However, differences in whole-brain functional networks in pre-reading children at risk for DD remain unexamined. The goal of this study is to investigate possible neural and behavioral pre-markers of DD in pre-reading children with (FHD+) and without (FHD-) a family-history of DD. **Methods:** 31 right-handed children (17 FHD+/14 FHD-; 5.5y) completed standardized psychometric testing. Functional magnetic resonance imaging was performed during rapid auditory processing. Stimuli were non-linguistic with a spectro-temporal structure comparable to that of consonant-vowel-consonant speech syllables, with either rapid or slowed frequency transitions. Participants were instructed to indicate the pitch of the stimulus. Random-effects analyses for rapid versus slow transitions were performed. **Results:** FHD+ children, compared to FHD- children, showed significantly reduced expressive language, phonological processing and rapid naming skills. Performance

inside the MR scanner indicated no significant group differences for pitch identification. However, preliminary imaging results directly comparing the two groups showed increased activation (FHD- > FHD+) in various brain areas including left prefrontal, bilateral auditory and bilateral inferior parietal regions (**Figure 1**). **Conclusion:** Our results suggest that pre-reading children with a family history of DD already show a disrupted response to rapid acoustic stimuli in similar brain regions as children and adults with a diagnosis of DD. A longitudinal follow-up study will determine whether these early differences in brain function can predict reading outcome. An early identification of children at risk is essential for developing and improving intervention programs which may prevent negative clinical, psychological and social outcomes of DD.

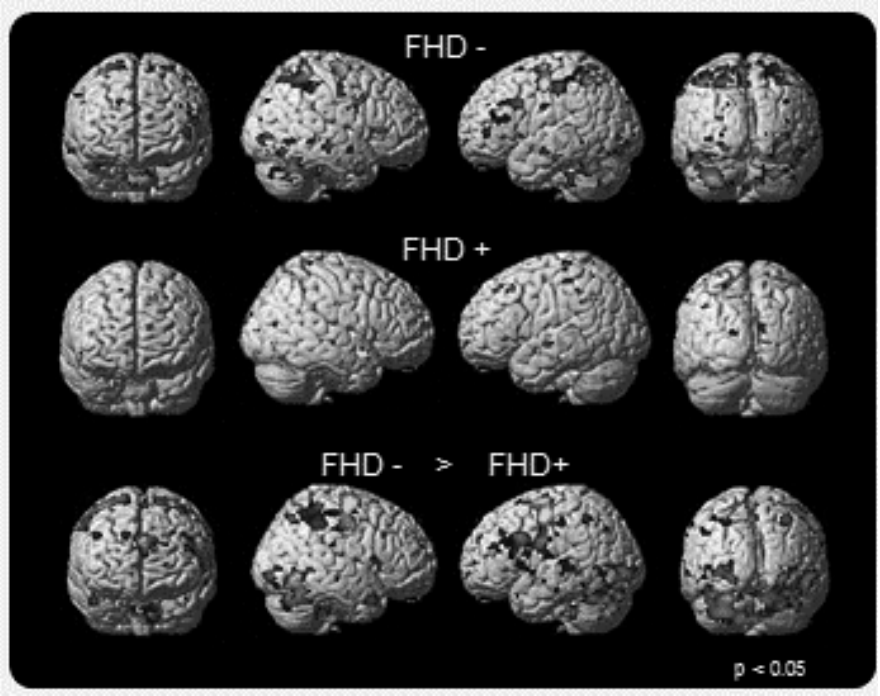

Figure 1. Preliminary imaging results show a characteristic pattern of brain activation in children without a family-history of dyslexia (FHD-) when processing rapid changes in sounds in various brain areas including left prefrontal, bilateral auditory and bilateral inferior parietal regions. This pattern is almost completely missing in children with a family-history of dyslexia (FHD+). Direct comparison of children with vs. children without a family-history of dyslexia confirms a disrupted neural response to rapid auditory processing in children with compared to

without a family-history of dyslexia (FHD- > FHD+) in various brain areas including left prefrontal, bilateral auditory and bilateral inferior parietal regions.

Aim4: *To examine structural differences between children with and without a family-history of dyslexia using voxel based morphometry (VBM). To test potential structure-behavior-relationships using correlational analysis.*

4.5 **STUDY 5:** STRUCTURAL BRAIN ALTERATIONS ASSOCIATED WITH DYSLEXIA PREDATE READING ONSET

Nora Maria Raschle, Maria Chang, Nadine Gaab

Children's Hospital Boston, Department of Medicine, Division of Developmental Medicine, Laboratories of Cognitive Neuroscience, 1 Autumn Street, Mailbox # 713, Boston, MA 02115, USA

Neuroimage. 2011 Aug1; 57(3), 742-9. Epub 2010 Sep 25.

4.5.1 ABSTRACT

Functional magnetic resonance imaging studies have reported reduced activation in parietotemporal and occipitotemporal areas in adults and children with developmental dyslexia compared to controls during reading and reading related tasks. These patterns of regionally reduced activation have been linked to behavioral impairments of reading-related processes (e.g., phonological skills and rapid automatized naming). The observed functional and behavioral differences in individuals with developmental dyslexia have been complemented by reports of reduced gray matter in left parietotemporal, occipitotemporal areas, fusiform and lingual gyrus and the cerebellum. An important question for education is whether these neural differences are present before reading is taught. Developmental dyslexia can only be diagnosed after formal reading education starts. However, here we investigate whether the previously detected gray matter alterations in adults and children with developmental dyslexia can already be observed in a small group of pre-reading children with a family-history of developmental dyslexia compared to age and IQ-matched children without a family-history (N=20/mean age: 5:9 years; age range 5:1–6:5 years). Voxel-based morphometry revealed significantly reduced gray matter volume indices for pre-reading children with, compared to children without, a

family-history of developmental dyslexia in left occipitotemporal, bilateral parietotemporal regions, left fusiform gyrus and right lingual gyrus. Gray matter volume indices in left emispheric occipitotemporal and parietotemporal regions of interest also correlated positively with rapid automatized naming. No differences between the two groups were observed in frontal and cerebellar regions. This discovery in a small group of children suggests that previously described functional and structural alterations in developmental dyslexia may not be due to experience-dependent brain changes but may be present at birth or develop in early childhood prior to reading onset. Further studies using larger sample sizes and longitudinal analyses are needed in order to determine whether the identified structural alterations may be utilized as structural markers for the early identification of children at risk, which may prevent the negative clinical, social and psychological outcome of developmental dyslexia.

4.5.2 INTRODUCTION

Developmental dyslexia, which affects 5-17% of all children, is a specific learning disability characterized by difficulties with accurate and/or fluent word recognition, poor spelling and decoding skills (Beitchman et al., 1986). Difficulties in reading are disproportionate to other cognitive abilities (such as IQ) and cannot be explained by poor vision, hearing difficulty or a lack of motivation or educational opportunities (World Health Organization, 1992). Familial occurrences and twin studies suggest that developmental dyslexia is highly heritable, occurring in up to 40% of individuals who have a first-degree relative with developmental dyslexia (Fisher and Francks, 2006; Smith et al., 1983). Several candidate susceptibility genes for developmental dyslexia have been reported (Galaburda et al., 2006). The majority of these genes are shown to be important for brain development and it has been suggested that developmental dyslexia may be caused by abnormal migration and/or maturation of neurons during early development (Galaburda et al., 2006). Developmental dyslexia can only be diagnosed after the onset of formal reading instruction (around second or third grade in the United States). However, identifying a child after reading onset limits the time available for early interventions that may prevent the serious clinical, psychological and social impact of developmental dyslexia.

Studies focusing on behavioral pre-markers of reading ability and disability have suggested that linguistic impairments such as deficits in language comprehension, phonological processing or impaired letter name knowledge prior to formal reading instruction predict reading ability in children with and without a family history of developmental dyslexia (e.g.; Flax et al., 2008; Gallagher, 2000; Pennington and Lefly, 2001; Puolakanaho et al., 2008; Scarborough, 1990; Snowling et al., 2003). Additionally, several studies have found deficits in rapid automatized naming prior to formal reading instruction which predict later reading abilities (De Jong and Van der Leij, 1999; Kirby et al., 2003; Kobayashi et al., 2005; Wolf, 1986; Wolf et al., 1986). Furthermore, research suggested that both phonological processing and rapid automatized naming contribute uniquely and substantially to word reading from grade 1 to grade 6 (Vaessen et al., 2009; Vaessen and Blomert, 2010).

Several studies have utilized brain measures to study young children at risk for developmental dyslexia and healthy controls. Electrophysiological differences have been reported for infants with familial risk for developmental dyslexia for basic auditory and language processing (e.g.; Guttorm et al., 2001; 2003; Pihko et al., 1999; Leppanen et al., 2002). However, to date only one study has reported neural predictors of reading abilities (Maurer et al., 2009) in children with and without a familial risk of dyslexia. In a 5-year longitudinal study, neurophysiological and behavioral measures obtained in 6 year old kindergarteners with and without a family history of dyslexia predicted reading outcome after reading instruction. Neurophysiological measures in kindergarten furthermore improved reading prediction in comparison to behavioral measures alone and were the only predictor for reading success in fifth grade.

Previous neuroimaging studies revealed differences in brain structure and function between school-age children and adults with a diagnosis of developmental dyslexia and controls. Using functional magnetic resonance imaging (fMRI), individuals with developmental dyslexia showed reduced activation during reading and reading related tasks in left-hemispheric occipitotemporal regions which correlated with reduced reading skills (Hoeft et al., 2007b; Temple, 2002; Specht et al., 2009). Structural magnetic resonance imaging (MRI) with voxel-

based morphometry (VBM) revealed decreased gray matter volume indices in individuals with developmental dyslexia, when compared to typical reading controls, in several brain regions such as left occipitotemporal and temporoparietal areas (Brambati et al., 2004; Brown et al., 2001; Eckert et al., 2005; Hoeft et al., 2007a; Kronbichler et al., 2008; Pernet et al., 2009; Silani et al., 2005), bilateral fusiform (Kronbichler et al., 2008) and lingual gyrus (Eckert et al., 2005) as well as the cerebellum (Brambati et al., 2004; Brown et al., 2001; Eckert et al., 2005). Moreover, gray matter volume indices in these areas were positively correlated with pre-reading and reading skills, such as timed and untimed (pseudo-)word reading (Kronbichler et al., 2008; Pernet et al., 2009; Silani et al., 2005; Steinbrink et al., 2008), phonological processing (Kronbichler et al., 2008; Pernet et al., 2009), spelling performance (Pernet et al., 2009) and rapid automatized naming (RAN) (Kronbichler et al., 2008). Similarly, white matter organization, as characterized by diffusion tensor imaging (DTI), is found to be weaker in left posterior brain regions in individuals with developmental dyslexia and correlate positively with reading skills, such as reading speed or word and pseudo-word reading (Klingberg et al., 2000; Silani et al., 2005; Steinbrink et al., 2008).

It remains unclear whether these morphological differences exist at birth, develop during the first few years of life, or are due to experience-dependent structural changes that occur after the onset of formal reading education. In the current study we utilized VBM (Ashburner and Friston, 2005) to investigate whether the previously reported differences in gray matter volume indices in individuals with developmental dyslexia can already be observed in a small group of five year old pre-readers with a family-history of developmental dyslexia.

4.5.3 METHODS

Subjects. 20 healthy, native English speaking children with (FHD+/n=10) and without (FHD-/n=10) a family-history of developmental dyslexia, have been included in the present analyses. All children are enrolled in our larger longitudinal study which also employs functional imaging, psychophysical measures as well as conducts genetic testing. FHD+ children (mean age 5 years and 11 months) had at least one first degree relative with a clinical diagnosis of developmental

dyslexia. Children with a family-history of reading difficulties, but no clinical diagnosis of developmental dyslexia in the family, were excluded from the study. FHD- children (mean age 5 years and 7 months) had no first degree relatives with developmental dyslexia and no self-reported history of reading difficulties or language delays in their families. Children were furthermore screened for hearing and vision difficulties, neurological disease or psychiatric disorders using a parent questionnaire. The two groups of FHD+ and FHD- children were matched by group for age, gender and non-verbal IQ (Kaufman Brief Intelligence Test, 2nd edition / (Kaufman and Kaufman, 1997)). Data obtained in the national early childhood longitudinal study (ECLS-K, kindergarten class of 1998-1999), indicate that by kindergarten entry only 2 % of all children are able to identify sight words and no more than 1% recognize words in context (Denton et al., 2000). Based on this study, only pre-reading children were enrolled in our study. During an initial telephone-/email-screening with the parents we screened for pre-reading status in all children. Only pre-reading children (parent report) who were planned to receive formal reading instruction within the next months were invited to take part in the study. Furthermore, the Word Identification subtest of the Woodcock Reading Mastery Test (WRMT; (Woodcock, 1998)) was administered to assure pre-reading status. For the Word Identification subtest the child is required to identify isolated words presented in the test booklet. For an answer to be scored as correct, the child must produce a natural or fluent reading of the word within about five seconds. Seventeen children (9 FHD+/8 FHD-) were not able to read a single word, two children (1 FHD+/1 FHD-) recognized two and one child (FHD+) recognized seven isolated words. All children were tested between May and November of their kindergarten entry year (based on the reading curriculum, children should be able to read first words by the end of November of their kindergarten year). This study was approved by the ethics committee of Children's Hospital Boston. Verbal assent and informed consent was obtained from each child and guardian, respectively.

Behavioral Group Characteristics. Participants were characterized with a test battery of standardized assessments examining language and pre-reading skills such as expressive and receptive vocabulary (Clinical Evaluation of Language Fundamentals (CELF Preschool 2nd edition;

(Semel et al., 1986)), phonological processing (Comprehensive Test of Phonological Processing (CTOPP); (Wagner et al., 1999)) and RAN (Rapid Automatized Naming Test; (Wolf and Denckla, 2005)). Additionally, potential confounders included socioeconomic status and home literacy environment. All participating families were given a socioeconomic background questionnaire (questions adapted from the MacArthur Research Network: http://www.macses.ucsf.edu/Default.htm) and answered questions concerning the home literacy environment (based on (Denney et al., 2001) as cited in (Katzir et al. 2009)). For a complete overview of SES and HLE questions see SI1 and SI2).

Imaging Procedure. For all participants an age-appropriate neuroimaging protocol was used, which included an intensive familiarization with the MRI equipment in a mock scanner area prior to the actual neuroimaging session (Raschle et al., 2009). T1-weighted MPRAGE MRI sequences were acquired on a Siemens 3 Tesla whole body scanner with the following specifications: 128 slices, TR 2000 ms; TE 3.39 ms; flip angle 9°; field of view 256 mm; voxel size 1.3 × 1.0 × 1.3 mm. Whole brain structural brain images were collected for all children between August and November prior to their or within the first few weeks of their first kindergarten year.

VBM Analysis and Statistics. We utilized optimized voxel-based morphometry (Ashburner and Friston, 2005), a whole-brain analysis technique, to examine differences in gray matter volume indices between pre-reading FHD+ and FHD- children. In particular, the VBM5.1 toolbox (http://dbm.neuro.uni-jena.de/vbm) was employed using SPM5 software (www.fil.ion.ucl.ac.uk/spm) executed in MATLAB (Mathworks, Natick, MA). All images were segmented, bias-corrected and spatially normalized to a customized pediatric brain template specific to the group's characteristics (e.g. age and gender) to account for brain size and development within our pediatric population (mean: 5 years and 9 months). The template was generated using Template-O-Matic, a toolbox to create customized brain templates of high quality, especially in smaller subject samples (Wilke et al., 2008). Using unified segmentation, the images were segmented into gray matter, white matter and cerebrospinal fluid. Data

quality was assured with a sample homogeneity test by plotting the standard deviation of the normalized, gray matter segmented brain volumes across all subjects. The covariance between each gray matter volume is hereby visualized using a boxplot and covariance matrices (for VBM manual and details see http://dbm.neuro.uni-jena.de/vbm). Finally, bias-corrected, whole brain Jacobian modulated images (preserving total gray matter volume) were smoothed with a 12-mm full width at half maximum isotropic Gaussian kernel (Ashburner and Friston, 2005).

Regional variations in gray matter volume indices (GMVI, corresponding to the percentage of gray matter in a given voxel) between FHD+ and FHD- children were calculated using a two-sample t-test. Statistical significance thresholds were applied at the voxel-level ($p<0.001$, uncorrected). Results for the whole brain analysis were obtained using non-stationary correction ($p<0.01$ cluster size extent value), which is essential to adjust cluster sizes according to local roughness (Hayasaka et al., 2004). To examine the relationship between structural and behavioral measures, we defined two main regions of interests. The ROIs were defined by a 8mm radius sphere, centered around parietotemporal and occipitotemporal activation peaks as identified in a meta-analysis of 35 neuroimaging studies of word and pseudoword reading (Jobard et al., 2003). They further overlap with the observed anatomical differences between pre-reading children with and without a family-history of developmental dyslexia in the current study. Using the brain imaging toolbox (BIT, Gabrieli Lab, Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA, USA) a parietotemporal ROI was created at x = -44 +/-4; y = -58 +/-5; z = -15+/-6 and a more occipitotemporal ROI at x = -60 +/-4; y = -41 +/-6; z = 25+/-6. The two ROIs were normalized to our customized pediatric template, which accounts for brain size and development within our pediatric population. Next, mean GMVIs of these ROIs were extracted for each individual. Finally, the average of GMVIs within each ROI for the whole experimental group (n=20; 10FHD+/10FHD-) was correlated with standardized behavioral measures, which have shown to predict reading ability: phonological processing (e.g. Flax et al., 2008; Gallagher, 2000; Pennington and Lefly, 2001; Puolakanaho et al., 2008; Scarborough, 1990; Snowling et al., 2003;) and RAN (De Jong and Van der Leij, 1999; Kirby et al., 2003; Kobayashi et al., 2005; Wolf, 1986; Wolf et al., 1986).

Statistical correlation analysis was performed using SPSS software package, version 16.0 (SPSS Inc., 1999). Significance thresholds of this ROI correlation analysis were corrected for multiple comparisons by controlling for the false discovery rate (FDR, Benjamini & Hochberg, 1995).

4.5.4 RESULTS

Demographics and Behavioral Data. Demographic characteristics of all participants are listed in Table 1. We observed significant differences in standardized behavioral assessments of RAN between children with a family history of developmental dyslexia (FHD+) compared to children without a family-history of developmental dyslexia (FHD-) ($p \leq 0.001$; Table 1). Mean scores of expressive and receptive language skills and phonological processing appeared to be lower in FHD+, compared to FHD-, children but did not reach significance ($p > 0.05$). There were no group differences in age ($p = 0.241$) and no group differences in verbal or non-verbal IQ (Verbal: $p = 0.489$/Non-verbal: $p = 0.452$). Furthermore, there was no significant difference ($p > 0.05$) in socioeconomic status (SES; e.g. parental education and total family income over the last 12 month) or home literacy environment (HLE; e.g. age of child when first read to, total number of adult or children books at home) between groups (Table 1, SI1 and SI2).

Table 1. Subject Demographics.

		FHD+	FHD-	*p* FHD+ vs. FHD-
N		10	10	**sig. 2-tailed** *Independent samples t-test*
Age (years)		5:11	5:7	0.241
Age (range in years)		5:5-6:5	5:1-6:2	
Behavioral Measures		**Mean ± SD**	**Mean ± SD**	**sig. 2-tailed** *Independent samples t-test*
CELF	Core Language	105.6 ± 8.9	109.9 ± 11.7	0.366
	Receptive Language [a]	105.3 ± 16.6	110.2 ± 10.8	0.455
	Expressive Language	102.1 ± 8.2	110.0 ± 13.0	0.121
	Language Content [a]	100.4 ± 11.9	110.1 ± 11.7	0.093
	Language Structure [a]	105.6 ± 11.8	109.5 ± 12.1	0.483
CTOPP	Elision	8.9 ± 1.8	10.2 ± 2.3	0.181
	Blending	10.7 ± 2.4	11.9 ± 1.6	0.199
	Non-Word Repetition	9.8 ± 2.5	10.8 ± 1.9	0.334
RAN	Objects	85.9 ± 11.0	107.5 ± 13.4	0.001*
	Colors	84.2 ± 11.1	110.1 ± 10.5	0.000**
KBIT	Verbal Ability	110.9 ± 10.4	113.7 ± 7.0	0.489
	Non-Verbal Ability	97.6 ± 8.4	100.9 ± 10.6	0.452
Socioeconomic Status and Home Language Environment		**Mean ± SD**	**Mean ± SD**	**sig. 2-tailed** *Independent samples t-test*
Parental Education [b]		6.2 ± 0.5	6.23 ± 0.7	0.749
Age (in months) of child when first read to		4.4 ± 5.0	9.8 ± 19.0	0.429
Someone at home reads to the child [hours/week]		2.7 ± 1.4	3.4 ± 1.7	0.336
		Mean Rank	**Mean Rank**	**sig. 2-tailed** *Kruskal Wallis test*
Income (total family income for last 12 months) [c]		8.83	9.19	0.865
Total number of parents/adult books at home [d]		9.72	9.28	0.844
Total number of children's books at home [d]		8.50	10.50	0.146

Measures (standard scores are reported)

[a] 10 FHD+/9 FHD- (One child did not finish all testing)

[b] Parental Education scores are calculated according to the 7-point Hollingshead Index Educational Factor Scale, summed for husband and wife and divided by two (Hollingshead, 1975).

[c] Scale where 1 = 50 000 - 74 999 $, 2 = 75 000 - 99 999 $, 3 = 100 000+ $

[d] Scale where 1 = 0-50books, 2 = 50-100 books, 3 = 100+ books

* P < .01; ** P < .001; two-tailed t-test; all other t-tests non-significant at threshold of P = .05

VBM. Voxel-based morphometry (VBM5) revealed significantly reduced gray matter volume indices (GMVIs) for FHD+ compared to FHD- children in left occipitotemporal area (LOT: x = -43, y = -66, z = 4), left and right temporoparietal regions (LTP: x = -57, y = -34, z = 26; / RTP: x = 46, y = -29, z = 24), left fusiform (LFG; x = -45, y = -60, z = -14) and right lingual gyrus (RLG; x = 23, y = -87, z = -11) at p<0.001 (corrected for non-stationarity; p<0.01) (see Figure 1 a-c and Table 2). The reported differences are displayed on our customized pediatric brain template and MNI coordinates also reflect our pediatric brain template generated with Template-O-Matic (Wilke et al., 2008), which optimally reflects our age range (mean: 5 years and 9 months) and hence the average brain development stage of our participant group. There were no significant differences in gray matter volume indices for the inverse contrast (FHD+ > FHD-; at p<0.001) and no differences in total gray matter (p=0.760) or total intracranial volume (p=0.772) between FHD+ compared to FHD- children.

Table 2. Significant differences in gray matter volume indices between FHD+ and FHD- children (at p<0.001 uc; adjusted for non-stationarity).

Brain region	Volume (mm)	Z score	Coordinates based on customized child template		
			X	Y	Z
Left occipitotemporal region (LOT)	144	4.51	-43	-66	4
Left temporoparietal regions (LTP)	767	4.27	-57	-34	26
Left fusiform gyrus (LFG)	116	3.83	-45	-60	-14
Right temporoparietal regions (RTP)	565	3.69	46	-29	24
Right lingual Gyrus (RLG)	517	4.09	23	-87	-11

Region of Interest (ROI) Analyses. Correlation analyses for standardized behavioral measures of phonological processing and RAN with GMVIs revealed significant positive Pearson correlations for the left temporoparietal and left occipitotemporal ROI with RAN (LTP: r=0.26, p=0.023/

LOT/LFG r=0.32, p=0.009; Figure 1 d-e). No significant correlations were found for the two ROIs with phonological processing. Because of the previously reported strong relationship between left occipitotemporal brain region and phonological processing in functional and structural studies (e.g. Hoeft et al., 2007b; Temple, 2002; Kronbichler et al., 2008; Pernet et al., 2009) we additionally extracted GMVIs from a non-independent ROI within our left occipitotemporal region (LOT) which exhibited significantly less gray matter volume in FHD+, compared to FHD-, children. GMVIs in LOT significantly correlated with phonological processing (r=0.25, p=0.024) and RAN (r=0.47, p=0.037).

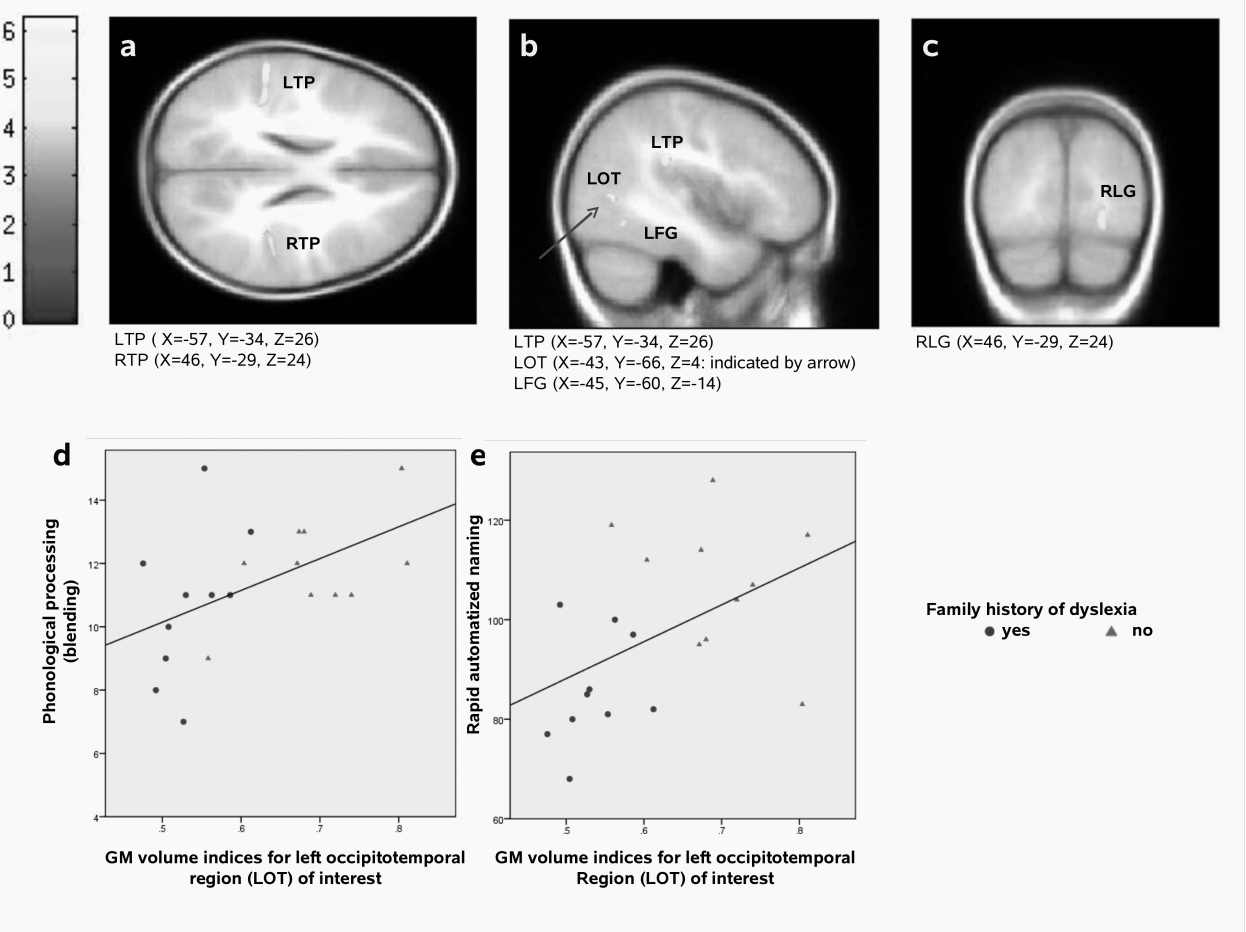

Figure1. [**a-c**] Statistical parametric maps showing brain areas with significant decreased gray matter volume indices in pre-reading FHD+ compared to FHD- children (a=axial, b=sagittal, c=coronal view). [**d-e**] Correlations between gray matter volume indices in the left parietotemporal (**d**) and left occipitotemporal (**e**) ROI and rapid automatized naming.

4.5.5 DISCUSSION

We observed reduced gray matter volume indices in a small group of pre-reading children with a family-history of developmental dyslexia, compared to children without a family-history, in brain areas known to be involved during reading and reading development (McCandliss and Noble, 2003; Schlaggar and McCandliss, 2007). These regions include the left occipitotemporal area, bilateral temporoparietal regions, left fusiform gyrus and right lingual gyrus. Furthermore, GMVIs within left hemispheric temporoparietal and occipitotemporal ROIs (created based on a meta-analysis on reading networks, Jobard et al., 2003) correlated with RAN skills. There are no significant differences in early literacy experience or socioeconomic background between children with compared to children without a family-history of developmental dyslexia, and therefore these variables do not account for the present findings.

The observed structural brain differences in pre-readers at risk for developmental dyslexia, compared to control children, correspond to brain regions that have been shown to differ (structurally and functionally) between individuals with developmental dyslexia and typical readers. In particular, our results are consistent with VBM studies that demonstrated gray matter differences in left occipitotemporal and bilateral temporoparietal areas (Brambati et al., 2004; Brown et al., 2001; Eckert et al., 2005; Hoeft et al., 2007a; Kronbichler et al., 2008; Pernet et al., 2009; Silani et al., 2005), fusiform (Kronbichler et al., 2008) and lingual gyrus (Eckert et al., 2005) in children and adults with a diagnosis of developmental dyslexia compared to typical-reading controls. Furthermore, our findings are supported by VBM and DTI studies demonstrating reduced white matter connectivity and white matter indices in left-hemispheric occipitotemporal regions in adults (Klingberg et al., 2000; Steinbrink et al., 2008) and children (Deutsch et al., 2005; Niogi and McCandliss, 2006; Rimrodt et al., 2009) with developmental dyslexia.

In contrast to VBM studies in individuals with developmental dyslexia, we did not observe structural brain alterations in left inferior frontal brain regions (Brown et al., 2001; Eckert et al., 2003) or the cerebellum (Brambati et al., 2004; Brown et al., 2001). However, we examined

structural brain alterations in pre-readers at risk for dyslexia as opposed to individuals with diagnosed developmental dyslexia or reading difficulties. It has been suggested that the alterations in frontal brain regions observed in children and adults with developmental dyslexia develop after the age of reading onset, mirroring the influence of experience and reading education (Hoeft et al., 2007a). Structural (Brambati et al., 2004; Brown et al., 2001) and functional MRI studies (Fulbright et al., 1999; Vlachos et al., 2007) have shown an involvement of the cerebellum during reading processes, such as word identification, phonological assembly and semantic processing. Our results complement these studies and suggest that structural differences in left occipitotemporal area, bilateral temporoparietal regions, left fusiform gyrus and right lingual gyrus in children with a family-history of dyslexia prior to reading-onset are likely a pre-existing biological deficit. Further alterations, such as those seen in frontal regions and the cerebellum, might reflect experience-dependent changes that typically coincide with the process of learning to read.

Previous research using fMRI shed light on the role of brain structures that significantly differ in individuals with developmental dyslexia when compared to typical readers. These studies indicate that the left occipitotemporal area is activated during tasks of phonological processing (Temple, 2002) and tasks requiring the visual analysis of letters and words (Cohen et al., 2003; McCandliss et al., 2003; Vinckier et al., 2007). The left fusiform gyrus is involved in rapid recognition of visual words (McCandliss et al., 2003; Vinckier et al., 2007) and gains particular importance during the later stages of reading development within the typical reading brain (McCandliss et al., 2003; Turkeltaub et al., 2003). The temporoparietal area is known to be important for the integration of letters and speech sounds (Van Atteveldt et al., 2004, 2007), a key skill for reading in starting readers. Furthermore, research has shown that individuals with developmental dyslexia display deficits in letter sound integration within the temporal-parietal network (Blau et al., 2009; Blau et al., 2010).

In the current study in a small group of pre-reading children, GMVIs extracted from left hemispheric parietotemporal and occipitotemporal brain regions also significantly correlated

with rapid automatized naming. Rapid automatized naming is commonly impaired in children and adults with dyslexia and was reported to be one of the main precursors of later reading ability in children (De Jong and Van der Leij, 1999; Kirby et al., 2003; Kobayashi et al., 2005; Wolf, 1986; Wolf et al., 1986). Furthermore, previous research reported significant correlations between gray matter volume in a left occipitotemporal region and digit naming (Kronbichler et al., 2008). Previosu research has suggested that RAN reflects the automation or efficiency of matching visual/orthographic units to their phonological counterparts (e.g.; Vaessen et al., 2009, Vaessen & Blomert, 2010) or the efficient retrieval of phonological codes (e.g. Wagner and Torgesen, 1987). This is in line with our finding which shows a correlation between brain regions previously reported to be involved in phonological processing and RAN.

Interestingly, the here reported GMVIs differences in the ROIs correlated with RAN, a task which in turn significantly differentiated our children with and without a family-risk of developmental dyslexia before reading onset. The here observed anatomical differences may therefore reflect either a family-history or behavioral risk for developmental dyslexia. Further studies need to determine whether pre-reading children without a family history of dyslexia but a strong behavioral risk for dyslexia (e.g.; as determined by psychometric testing) also display the here observed anatomical alterations.

Several studies have shown a reduction of gray and white matter in children and adults with DD which correlate with phonological processing (e.g. Kronbichler et al., 2008; Pernet et al., 2009) and correlations between functional differences in occipitotemporal and parietotemporal regions and phonological skills have also been reported (Hoeft et al., 2007b; Temple, 2002; Specht et al., 2009). In our present study we only observed a significant correlation between gray matter volume indices in the left occipitotemporal area (LOT) and phonological processing in a ROI which was defined by our observed anatomical differences but not when using independent ROIs defined by coordinates from previous publications which reported a similar correlation or meta-analysis. Therefore, the results of this analysis need to be interpreted with caution (see discussion by Poldrack and Mumford, 2009; Vul et al. 2009;). Although this lack of

a relationship between phonological skills and GMVI in left hemispheric regions in our sample may suggest that this relationship develops after reading onset or that RAN has a higher specificity at this age, there may be a methodological explanation for the missing correlation. In the present study, a pediatric template was utilized and previously reported results were reported for adult templates. Although independent ROIs can be normalized to the pediatric template (as performed here), the areas within occipitotemporal and parietotemporal regions that exhibited a difference in GMVIs between the two groups is relatively small and therefore ROIs defined based on coordinates from previous papers (with adult templates) were most likely not targeting the appropriate areas in our age group of pre-readers.

A Comprehensive Model of Dyslexia

Progress toward understanding developmental dyslexia has come from multiple levels. It has been suggested that developmental dyslexia may be a developmental disorder of genetic origin with a neurobiological basis (Galaburda et al., 2006; Silani et al., 2005). In line with the most recent neurobiological and genetic findings, our results support a comprehensive model of developmental dyslexia which incorporates variant function in genes involved in brain development, structural and functional brain alterations and pre-reading skills (Galaburda et al., 2006). To date, several genes (e.g.; ROBO1, DCDC2, DYX1C1, KIAA0319) have been reported to be candidates for dyslexia susceptibility and it has been suggested that the majority of these genes plays a role in brain development (Galaburda et al., 2006; Hannula-Jouppi et al., 2005; Meng et al., 2005; Paracchini et al., 2006). Since the structural alterations revealed in the present study predate the onset of formal reading instruction and as there are no significant group differences in socioeconomic status or home literacy environment, it can be hypothesized that genetic factors critical for brain development are responsible for the observed cortical alterations. More specifically, the cortical alterations in pre-reading children at risk for developmental dyslexia may originate from abnormal migration and/or maturation of neurons during early development which may lead to altered functional brain circuits and result in impaired pre-reading and reading skills (Galaburda et al., 2006). Interestingly, we observed

reduced and not increased gray matter indices in children with compared to without a family history of developmental dyslexia which speaks against effects of synaptic pruning at this young age where one would expect increased abnormality being associated with increased gray matter in certain cortical areas. Our reduced gray matter findings support previous hypotheses that reading disabilities, such as developmental dyslexia, are characterized by neural migration failure (e.g.; Chang et al., 2005, 2007; Galaburda et al., 2006) and are further in line with the finding that four of the main candidate suscebtibility genes (DYX1C1, KIAA0319, DCDC2, ROBO1) are linked to neuronal migration and other developmental processes (Galaburda et al., 2006). Furthermore, deviations in the migration of neurons from proliferative zones towards the cortex have also been found in post-mortem examination of individuals with developmental dyslexia (Galaburda, 1985) and reading and processing speed deficits have been reported for patients with neuronal migration disorder of periventricular nodular heterotopia (Chang et al., 2005).

Follow-up studies in young infants with and without a family history of developmental dyslexia may help to explain the underlying developmental mechanism for the here observed reduced gray matter indices in 5 year olds. Further examinations of models incorporating genetic vulnerability, structural and functional neuroimaging measures, and behavioral skills will be crucial for a complete understanding of the etiology of developmental dyslexia.

Implication for Educational Neuroscience

The present study in a small sample size demonstrates that the previously reported differences in gray matter volume indices in individuals with dyslexia can already be observed in a small group of five year old pre-readers with a family-history of developmental dyslexia. Future research using larger sample sizes and longitudinal designs are needed to determine if the observed structural alterations may be used as early indicators of developmental dyslexia. Especially longitudinal designs are necessary since not all children with a family history of developmental dyslexia will develop dyslexia and even some of the FHD- children may develop dyslexia. Our findings are in line with a 5-year longitudinal Swiss study by Maurer and

colleagues (2009). They reported that neurophysiological measures obtained at age 6 in kindergarten did not only predict reading after school-onset, but also improved the behavioral prediction of later reading skills and remained the only predictors of reading success in fifth grade. To date, studies focusing on the early detection of children at risk for developmental dyslexia have mainly centered on behavioral correlates of reading abilities, such as phonological processing (e.g.; Flax et al., 2008; Gallagher, 2000; Pennington and Lefly, 2001; Puolakanaho et al., 2008; Scarborough, 1990; Snowling et al., 2003;) language comprehension (Flax et al., 2008) and RAN (De Jong and Van der Leij, 1999; Kirby et al., 2003; Kobayashi et al., 2005; Wolf, 1986; Wolf et al., 1986). However, the feasibility of these behavioral correlates as effective screening measures remains a challenge (Gabrieli, 2009).

In this neuroimaging study, the focus on an understudied age group (pre reader to beginning readers) within the dyslexia population is highly significant as it provides an opportunity to examine potential predictors for an age group for which intervention might be most efficacious. For example, it has been shown that , children with learning disabilities are less likely than their peers to enroll in programs of higher education (Wagner, 1993) or complete high school (Marder, 1992) and are more likely to enter the juvenile justice system (Quinn, 2001). Early identification of predictors of reading disability in pre-reading children offers a chance to eliminate these significant personal and social costs. A modified approach to the way we teach children how to read must include early identification and the development of early preventive strategies. The identification of a child with reading disabilities in mid-elementary school may be too late. By this stage, the delayed development of reading has already affected children's vocabulary skills (Cunningham and Stanovich, 1991), motivation to read (Oka and Paris, 1986), thus leading to missed opportunities for the development of comprehension strategies (Brown et al., 1986). Studies have shown that children who are weak readers at the end of first grade remain poor readers by the end of elementary school (Francis and Shaywitz, 1996; Torgesen and Buress, 1998). Improved early identification of children at risk (behavioral or family risk) using neural pre-markers may further lead to changes in educational policies and will make it

possible to assign independent educational plans and customized curriculums for children at risk prior to formal schooling.

4.5.6 CONCLUSION

Structural brain alterations have previously been observed in children and adults with developmental dyslexia. Developmental dyslexia can only be diagnosed after formal reading instruction begins. However, our findings in a small group of pre-reading children demonstrate that previously described gray matter alterations in children and adults with developmental dyslexia in parietotemporal, occipitotemporal brain areas and left fusiform and right lingual gyrus are already observable in pre-readers with a family-history of developmental dyslexia and correlate with pre-reading skills. These findings cannot be explained by differences in socioeconomic background or early literacy experiences. This discovery suggests that structural alterations in developmental dyslexia may be present at birth or may develop in early childhood. Future research using larger sample sizes and longitudinal designs are needed to determine whether these structural alterations may be utilized for the identification of children at risk for developmental dyslexia in infancy and/or early childhood.

4.5.7 ACKNOWLEDGMENTS

This research was funded by the Charles H. Hood Foundation, a Children's Hospital Boston pilot grant, the Swiss National Foundation and the Janggen-Pöhn Stiftung (N.M.R.)

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Supplementary material is available in the appendix.

Aim5: *Here we aimed to investigate whether voice-specific areas in the human brain are already developed in pre-school children and whether they correspond to areas found in adolescence and adults.*

4.6 **STUDY 6:** VOICE SPECIFIC REGIONS IN PRE-SCHOOL AGED CHILDREN

Paper in preparation

Specialization of the right anterior superior temporal sulcus during voice-identification in five-year old children – an fMRI study

Raschle, NM & Gaab N (2011)

Background: The human voice is a necessary instrument of communication, carrying both speech and non-speech information. Voice perception and discrimination are crucial tools of survival for any given species on earth and it has been suggested that there are voice-specific regions in the brain of animals (e.g. [1,2]) as well as human beings [3,4,5]. In particular, the right anterior part of the superior temporal sulcus (STS) in humans has shown to be involved during the identification of voice-specific auditory material [4]. However, due to practical and technical challenges of imaging infants [6], most studies evolving around the study of human voice processing have been conducted in adults. Even though there is behavioral and electrophysiological evidence for an involvement of the right superior temporal sulcus during voice processing tasks in newborns and younger children, no study to date has used functional neuroimaging in pre-school children examine brain areas responsible for the processing of voice-specific information as identified in older children and adults. **Methods:** Twenty healthy, native English speaking children (average age 5.8 years), with no neurological or psychological history, have been included in the present analysis. All children were characterized with a standardized test battery assessing language and pre-reading skills as well as IQ. Each child performed two consecutive fMRI runs, a voice-matching task (VM; indicate whether two object words spoken in a male or female voice match) and a first-sound matching task (FSM; indicate whether the first sound of two object-words match). Both tasks were contrasted with a rest

condition (fixation cross). Contrast images (One sample t-tests) for VM>Rest, FSM>Rest and VM>FSM were obtained and a regions of interest analysis based on previously identified voice-specific brain region in adults [4] has been performed. Results: Pre-school children with average pre-reading, language skills and IQ are utilizing the right anterior part of the STS during tasks of speaker-voice identification. An independent region of interest analysis furthermore shows that the amount of brain activity in the right anterior STS is generally activated during auditory tasks including human. However, the activity in this region increases when children are focusing more on speakers voice then verbal content (VM>FSM; see also Figure 1 and Table1). **Conclusion**: This suggests that there are already brain areas specialized for the processing of voice-specific information in five year old children. Voice-specific areas in pre-school children further correspond to those identified in typical adults. Future studies will be able to further characterize the precise development and specialization of this brain area for the processing of voice identity.

[1] Belin, 2006; [2] Petkov et al., 2008; [3] Belin & Zatorre, 2003; [4] Von Kriegstein et al., 2003; [5] Kriegstein & Giraud, 2004; [6] Bookheimer, 2000

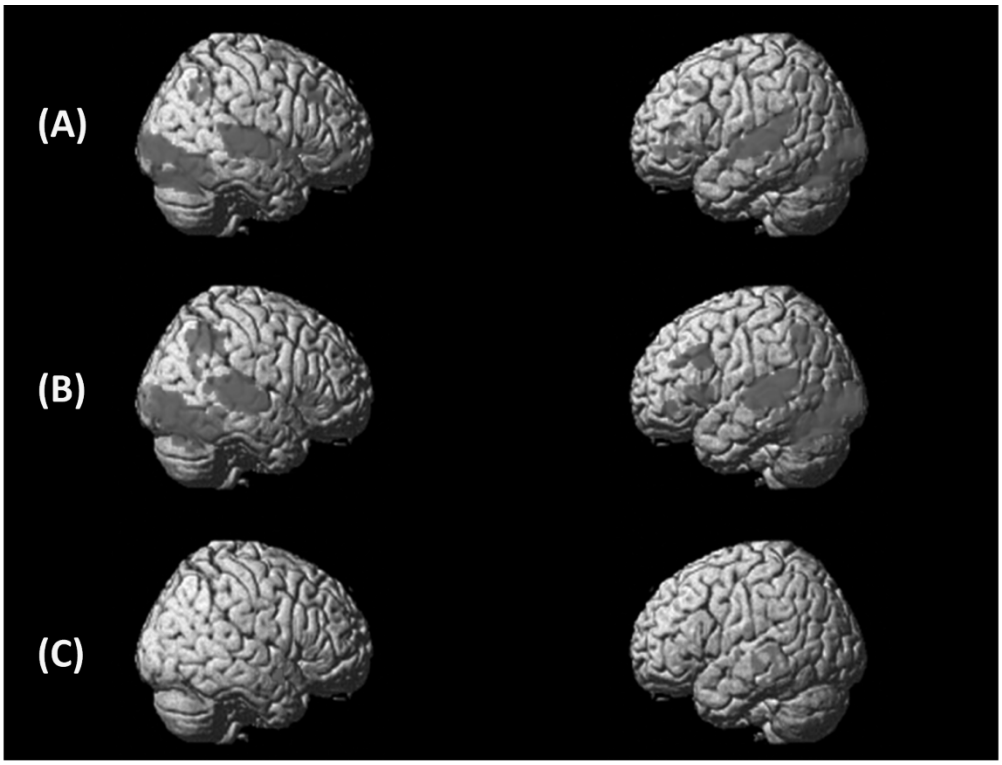


Figure 1. Cerebral regions activated when focusing on (**A**) speakers voice (Voice Matching > Rest) or (**B**) verbal content (FSM > Rest). Brain regions activated when focusing more on speaker voice than verbal content of spoken object words (**C**) VM > FSM ($p<0.005$; $k=10$).

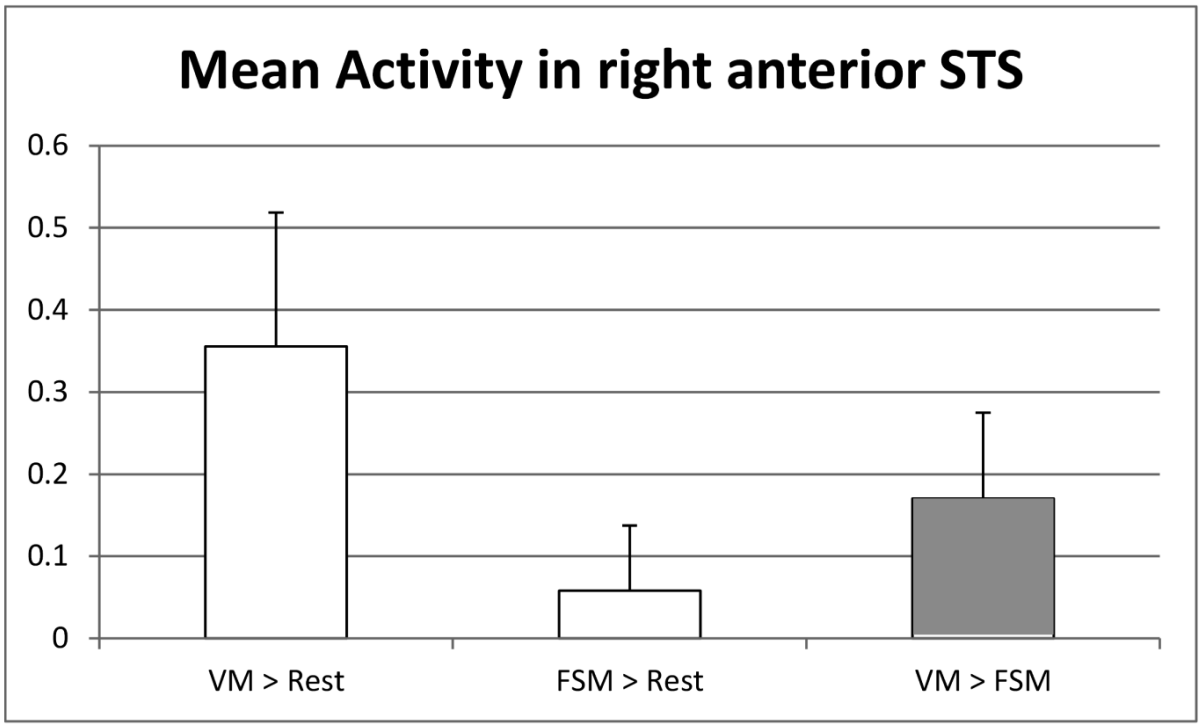


Table 1. Mean brain activation (weighted parameter estimates) in right anterior STS when focusing on speakers voice (Voice Matching > Rest; **Fig.1A**), verbal content (FSM > Rest; **Fig1B**) and when focusing more on speaker voice than verbal content of spoken object words (VM > FSM; **Fig1C**).

5 GENERAL DISCUSSION

To date there is a lot known about the behavioral and anatomical signature of children and adults with a diagnosis of dyslexia. However, the current literature reveals a series of unanswered key questions regarding the development of this disability. The present work aimed to investigate for the first time behavioral, structural and neuronal pre-markers of developmental dyslexia in children prior to reading onset. For this purpose we designed two initial studies, which were focused on the development and implementation of a new neuroimaging protocol suitable for young children. Next, we employed a multi-level approach using functional and structural brain indices, and psychometric and psychophysical measures to assess children with and without a risk for dyslexia prior to school onset. Using fMRI the neural signatures of pre-reading children at risk for dyslexia were here revealed in two studies examining phonological and rapid auditory processing. A separate study was designed to provide insight into the structural brain basis of children with and without a family-history of dyslexia prior to reading onset. Additionally, we examined the development of voice-specific regions in the human brain in typical developing 5-year olds.

The first aim of this thesis was the implementation of a child-friendly imaging protocol, which allows researchers and clinicians to perform structural and functional MRI in non-sedated children and/or infants (**Study1 and 2**). The protocol introduced in **Study1** has successfully been used in over a hundred child-imaging sessions in our laboratory. Data obtained in a sample of 4.9-6.3 year old pre-school children indicates that over 95% of all participants have completed a neuroimaging session composed of mock scanner training and actual imaging (Raschle et al., 2009). The described guidelines and tools may be applicable to pediatric neuroimaging that is reaching beyond the purpose of brain research, including the image acquisition of various body parts essential for clinical or research purposes.

The second and third aims of the current thesis were to investigate the neural correlates of phonological and rapid auditory processing in pre-reading children with and without a family-

history of dyslexia. Phonological processing deficits are the most common reported behavioral characteristics of individuals with dyslexia (Juel, 1988, Liberman et al., 1989, Ramus, 2003, Vaessen et al., 2009) and can already be found in children prior to literacy acquisition (Stanovich and Siegel, 1994, Pennington and Lefly, 2001, Snowling, 2003, Flax et al., 2009). However, researchers debate whether the phonological processing deficits observed in individuals with dyslexia constitute a so-called core deficit or whether there might be a more fundamental disability, such as in the processing of rapidly presented auditory material (McArthur and Bishop, 2001, Tallal, 2004, Tallal and Gaab, 2006).

Here (**Study3 and 4**) we provide behavioral and imaging evidence for a disruption of the neural networks of phonological, as well as rapid auditory processing, in children at risk for developmental dyslexia prior to reading onset. In line with neuroimaging research in children and adults with a diagnosis of dyslexia (Paulesu et al., 1996, Shaywitz et al., 1998b, Shaywitz et al., 2002, Hoeft et al., 2007a), our **Study3** shows that pre-reading children at risk for dyslexia show a hypoactivation during phonological processing in left hemispheric occipitotemporal and temporoparietal brain areas when compared to typical developing controls. Furthermore, there is a causal relation observable between neuronal activation within left lingual as well as superior temporal/postcentral gyrus and phonological processing skills in all children. However, only children with a family-history of dyslexia show an additional correlation between brain activity in middle temporal gyrus and phonological processing.

Similarly, in line with neuroimaging research in children and adults with a diagnosis of dyslexia (Ramus, 2003, Tallal, 2004, Tallal and Gaab, 2006, Gaab et al., 2007), **Study4** shows that there is a disruption in the neuronal response during rapid auditory processing in pre-reading children with a family history of dyslexia when compared to typically developing controls. This is in line with studies demonstrating neural differences for processing the rapidity of auditory material in children and adults with developmental dyslexia (Ramus, 2003, Tallal, 2004, Tallal and Gaab, 2006, Gaab et al., 2007), which can be ameliorated by training (Gaab et al., 2007).

Functional disruptions in reading and reading-related networks in children and adults with a diagnosis of dyslexia have been complemented by anatomical atypicalities. Morphological abnormalities have previously been identified in children and adults with dyslexia using voxel-based morphometry (VBM) and revealed differences in a network of brain areas including left occipitotemporal and temporoparietal areas (Brown et al., 2001, Brambati et al., 2004, Eckert et al., 2005, Silani et al., 2005, Hoeft et al., 2007a, Kronbichler et al., 2008, Pernet et al., 2009), bilateral fusiform (Kronbichler et al., 2006) and lingual gyrus (Eckert et al., 2005) as well as the cerebellum (Brown et al., 2001, Brambati et al., 2004, Eckert et al., 2005). The fourth aim of the current thesis was directed towards the investigation of structural characteristics of children at risk for dyslexia before reading instructions start. As our findings (**Study5)** demonstrate, differences in gray matter volume indices can already be identified in pre-reading children with a family-history of dyslexia when compared to those without in brain areas that correspond to findings in adults and children with a diagnosis of dyslexia. Atypical brain morphology has been reported in brain regions including left occipitotemporal, bilateral parietotemporal regions, left fusiform gyrus and right lingual gyrus. Gray matter volume indices in left hemispheric occipitotemporal and parietotemporal regions of interest furthermore show a positive correlation with behavioral measures of rapid automatized naming.

5.1 THE PRE-READING BRAIN OF CHILDREN AT RISK FOR DYSLEXIA

Figure 1 (page 90) contains on the left an overview about the major circuits involved during reading and reading-related tasks as seen in typical reading children and adults (graphic adapted from http://www.waece.org/cd_morelia2006/ponencias/stoodley.htm). This network includes posterior (ventral and dorsal) as well as anterior areas of the brain. On the right side, findings of the current thesis work, which is focusing on functional (phonological/rapid auditory processing) and structural characteristics in pre-reading children at risk for developmental dyslexia when compared to typical developing controls, are summarized. Our findings demonstrates that there are already detectable differences in the brain structure and function of posterior dorsal as well as ventral (pre-)reading networks in children with a familial risk for

dyslexia prior to reading onset. The seat of the identified atypical brain structures and functions corresponds to regions identified in children and adults with a diagnosis of dyslexia.

The presented neuronal and structural atypicalities in children at risk for developmental dyslexia have been complemented by correlational analysis linking the areas of impairment to standardized behavioral assessments of phonological processing and rapid automatized naming. **Table 2** provides a summary of the current findings, which allows us to consider a link between brain structures and functions.

Converging evidence from numerous research studies about reading, reading disability and dyslexia have implicated a left-hemispheric posterior (with a ventral and dorsal component) and a more anterior circuit to be crucial for successful reading acquisition (for a review see for example (Pugh et al., 2000)). Our findings provide evidence for the presence and importance of this left-hemispheric reading network, even before reading onset. In the upcoming section, the different parts of this (pre-)reading network are discussed.

Reading network in the left hemisphere

Anterior

Higher level sound processing

Posterior

Dorsal system:
Phonological processing
Grapheme-Phoneme Mapping

Ventral system:
Visual word form area
Letter recognition

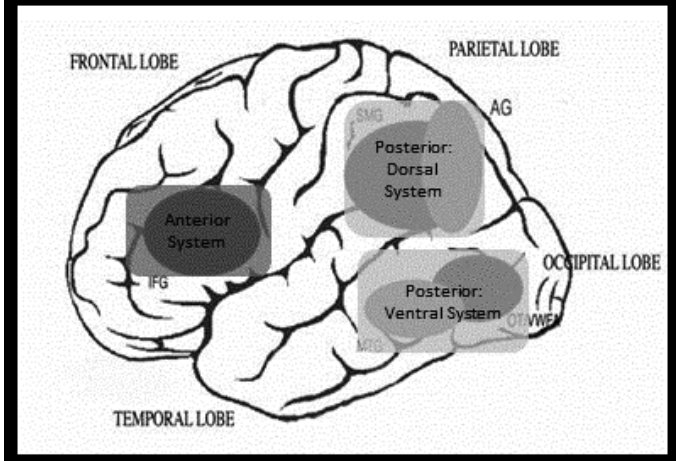


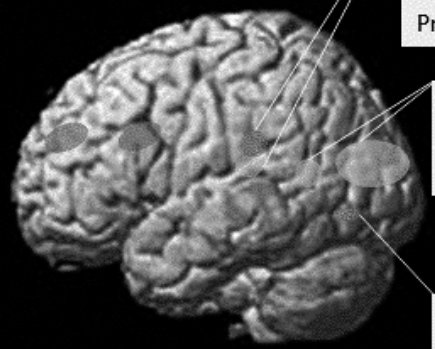
Image: http://www.waece.org/cd_morelia2006/ponencias/stoodley.htm

Areas of hypoactivations and/or structural abnormalities in pre-reading children at risk for dyslexia (Studies 3-5)

Areas of hypoactivations during phonological processing

Areas of reduced GMVIs

Areas of hypoactivations during rapid auditory processing



Correlational Analysis
GMVIs with RAN
Neural Activity and phonological Processing skills

Correlational Analysis
Neural Activity and phonological processing skills

Correlational Analysis
GMVIs with RAN

Independent ROI in LOT:
GMVIs with RAN
GMVIs with phonological processing

Table 2. Structure/Function-Relationships between brain areas and language abilities, identified during the present thesis work.

Left-hemispheric Regions of Interest	Group	Task	Structure/Function-Relationship
OCCIPITOTEMPORAL (POSTERIOR VENTRAL)			
Lingual Gyrus x = -16; y = -86; z = -10	FHD+ FHD-	FSM FSM	brain activation and phonological processing (p=0.016) brain activation and phonological processing (p=0.003)
TEMPOROPARIETAL (POSTERIOR DORSAL)			
Superior Temporal/Postcentral Gyrus x = -60; y = -28; z = 14	FHD+ FHD-	FSM FSM	brain activation and phonological processing (p=0.018) brain activation and phonological processing (p=0.013)
Middle Temporal Gyrus x = -48; y = -56; z = 6	FHD+ FHD-	FSM FSM	brain activation and phonological processing (p=0.003) -
Left-hemispheric Regions of Interest	**Group**	**Task**	**Structure/Function-Relationship**
OCCIPITOTEMPORAL (POSTERIOR VENTRAL)			
Independent ROI (Jobard et al., 2003) x = -60 +/-4; y = -41 +/-6; z = 25+/-6	All		GMVIs and RAN (p=0.009)
Non-Independent ROI x = -43; y = -66; z = 4	All		GMVIs and RAN (p=0.037) GMVIs and phonological processing (p=0.024)
TEMPOROPARIETAL (POSTERIOR DORSAL)			
Independent ROI (Jobard et al., 2003) x = -44 +/-4; y = -58 +/-5; z = -15+/-	All		GMVIs and RAN (p=0.023)

5.1.1 LEFT-HEMISPHERIC POSTERIOR PRE-READING NETWORKS

Left temporoparietal brain regions (posterior dorsal) have shown to be involved during the integration of letters and speech sounds (van Atteveldt et al., 2004). This area is typically activated by typical reading children and adults during tasks requiring phonological analysis of spoken or written words (for reviews (Pugh et al., 2000, Sandak et al., 2004, Schlaggar and McCandliss, 2007)). The dorsal pathway has been implicated during segmental sublexical processing of speech and non-speech sounds (Zaehle et al., 2008). Additionally, a hypoactivation in temporoparietal brain areas is characteristic for individuals with dyslexia and seems to reflect an inability in grapheme-phoneme mapping (Shaywitz et al., 1998b, Paulesu et al., 2001, Shaywitz et al., 2002, Gaillard et al., 2003, Hoeft et al., 2007a). In the current thesis work, we could demonstrate that there are differences in the brain function (phonological processing) as well as morphonolgy (GMVIs) in temporoparietal areas in children at risk for dyslexia compared to those without prior to reading onset. Correlational analysis have further

linked temporoparietal brain regions to abilities of phonological processing and rapid automatized naming.

Left occipitotemporal brain regions (posterior ventral) have shown to be involved during the processing of words and pseudowords (for reviews (Pugh et al., 2000, Sandak et al., 2004, Schlaggar and McCandliss, 2007)) and is thought to be the location of a memory-based word identification system, the so called visual word form area (Cohen et al., 2002). In the current thesis work, we could demonstrate that ther are differences in the brain function (phonological processing) as well as morphology (GMVIs) in occipitotemporal areas of children at risk for dyslexia compared to those without prior to reading onset. Again, correlational analysis have further linked occipitotempora brain regions to abilities of phonological processing skills and rapid automatized naming.

An interesting observation derives from looking at children with and without a familial risk for developmental dyslexia independently. When looking at the ventral and dorsal pre-reading networks of children with and without a family-history of dyslexia, it becomes visible that the tuning for auditory phonological processing may be developed differently in children with and without a family-history of dyslexia. Children with a family-history of dyslexia show a range of, but predominantly negative activation within dorsal and ventral pre-reading networks during phonological processing tasks. Children with a family-history also show a range, but predominantly positive activation in thes brain areas. In both groups, brain activation in left lingual and superior temporal/postcentral gyrus positively correlates with phonological processing abilities, which indicates the importance of this areas for phonological processing (more brain activity along with higher skill levels). However, only children with a family-history of dyslexia show additional correlations between phonological processing skills and brain activity in left middle temporal gyrus. Therefore, we suggest that tuning for auditory phonological processing in left lingual and superior temporal/postcentral gyrus is still emerging in all children, while specialisation in middle temporal gyrus has been reached for children without a family-history of dyslexia (predominant positive brain activation in this area during

phonological processing, but no correlation) but is still developing in those with (predominantly negative brain activation and positive correlation. The current findings are in line with research suggesting a dissociation between the development of dorsal and ventral brain areas, with more dorsal regions specializing earlier then more ventral areas (Sandak et al., 2004).

5.1.2 LEFT-HEMISPHERIC ANTERIOR PRE-READING NETWORKS

Anterior aspects of the left-hemispheric reading network have been attributed to higher level sound processing. For example Kovelman et al. (2011) could show that in school-aged children, but not children with dyslexia of the same age, the left dorsolateral prefrontal cortex was involved during tasks that required explicit phonological judgments (Kovelman et al., 2011). Furthermore, hyperactivations in anterior prefrontal brain regions in individuals with dyslexia during reading and reading-related tasks have been identified and it was suggested that these overactivations may represent compensatory mechanisms to make up for the failing of the left-hemispheric posterior reading network (Shaywitz et al., 1998a, Pugh et al., 2000, Temple et al., 2003, Eden et al., 2004, Hoeft et al., 2007a, Hoeft et al., 2011). In line with this, Hoeft and colleagues (2011) showed that children with dyslexia demonstrate relative overactivation during tasks of phonological awareness in right prefrontal brain regions, most likely due to compensatory mechanism. Additionally, future reading gains in children with dyslexia were best predicted by a combination of right superior white matter organization indices and greater right frontal activation during a phonological awareness task. This indicates that the more children with dyslexia use right frontal brain areas to compensate for the failing of the left-hemispheric reading network, the more likely they are to progress in reading (Hoeft et al., 2011). In **Study4** we could show that pre-reading children with a family-history of dyslexia show a dysfunction in let prefrontal brain areas during rapid auditory processing when compared to typical pre-reading controls. Unlike research in individuals with a diagnosis of dyslexia (Brown et al., 2001, Eckert, 2003) we did not find a reduction of gray matter volume indices in children with a familial risk of dyslexia prior to reading onset (**Study5**). Furthermore, there were no hyper- or

hypoactivations during phonological processing or rapid auditory processing in children with a risk for dyslexia prior to reading onset (**Study3 and 4).**

We conclude that anterior aspects of the left-hemispheric reading network, known to be involved during the processing of rapid changes in sounds, are already disrupted in children with a family history of dyslexia prior to reading onset. However, any compensatory mechanisms seen in children and adults with a diagnosis of dyslexia during reading and reading related tasks in anterior brain regions are not yet detectable in children at risk for dyslexia prior to reading onset. Therefore, hypoactivations in prefrontal brain areas seem to be characteristic for children at risk for dyslexia during rapid auditory processing. However, hyperactivations in dyslexia in anterior brain regions during reading and reading-related tasks, such as phonological processing, are a characteristic that only develops past reading onset, most likely as a compensation for reading failure.

5.2 A COMPREHENSIVE MODEL OF DYSLEXIA

For all our studies, the groups under investigation are matched for age and IQ. Using adequate questionnaires, we ruled out the influence of possible of confounding factors such as differences are independent of home literacy environment or socioeconomic status. Since all participants were tested for pre-reading status, we can conclude that structural, functional and behavioral differences cannot be accounted for by reading failure in the group of children at risk for dyslexia. Thus the underlying mechanisms leading to the neuronal disruption in networks of phonological processing, rapid auditory processing as well as structural abnormalities in pre-reading children with a family-history of dyslexia must either develop within the first few years of life or may even be present at birth. In all studies we showed characteristic patterns of significantly lower standard scores in children with compared to without a family-history of dyslexia on assessments of phonological processing skills, expressive and receptive language as well as rapid automatized naming. This finding is in line with findings of various behavioral studies in adults and children with a diagnosis of dyslexia or children at

risk for reading disability/dyslexia (for reviews see for example Felton et al., 1990; Shaywitz et al., 1998b; Flax et al., 2009 Gabrieli, 2009), and can thus can be interpreted as evidence for the representativeness of the chosen groups of children with compared to without a family-history of dyslexia (distinct deficits in children at risk for dyslexia).

Overall, our results support a comprehensive model for dyslexia which examines the link between variant function in genes involved in brain development, structural and functional brain alterations and pre-reading skills (Galaburda et al., 2006). Because our findings predate the onset of formal reading instruction, it can be hypothesized that genetic factors critical for brain development are responsible for the observed cortical alterations. More specifically, the cortical alterations in pre-reading children at risk for dyslexia may originate from abnormal migration and/or maturation of neurons during early development which may lead to altered functional brain circuits and result in impaired (pre-)reading skills (Galaburda et al., 2006). Further examinations of models incorporating genetic vulnerability, structural/functional neuroimaging measures and behavioral skills will be crucial for a complete understanding of the etiology of dyslexia.

5.3 CENTRAL PUBLIC HEALTH ISSUE – NEUROSCIENCE AND EDUCATION

Although neuroscience is a relatively new technique, it has enabled us to study brain processes in the conscious human being and has informed us tremendously in the attempt to understand very complex cognitive processes; exemplary language, speech and reading acquisition (Goswami, 2004). Consequently, there have been strides towards bridging the knowledge of different domains, in particular neuroscience and education (e.g. (Goswami, 2004, 2006, Gabrieli, 2009)). How valuable the knowledge gained through cognitive neuroscience for educational psychologist is, may still be under discussion (e.g. Stanovich, 1998; (Goswami, 2004, 2006, Hirsh-Pasek and Bruer, 2007). A major caveat of the pairing of neuroscience and education is the possible “misuse” of science within education. For example there are various known neuromyths influencing practices within U.S. classrooms (e.g. the “arrangement of left-

/right-brained children within classrooms" probably based on an over-literal interpretation of hemispheric specialization; (Goswami, 2006). However, there are possibilities to enhance the knowledge of our educational practice, for example through the early detection of children with developmental disabilities, such as dyslexia. In particular, an early identification of predictors for reading ability and disability in pre-reading children is essential for the development of novel as well as the evaluation and improvement of existing remediation programs. Identifying children at risk for dyslexia at an early stage could therefore reduce any associated costs and improve the effectiveness of programs (early start, accelerated remediation, shorter program duration). Previous research has shown that children with developmental dyslexia significantly gain from effective remediation programs. For example in a behavioral study, the use of a three-month long visual-auditory multimedia program led to improved writing skills in children with and without developmental dyslexia (Kast et al., 2007). Similarly, an 8-week phonologically based intervention program in children with developmental dyslexia led to performance improvements, accompanied by neural changes in bilateral parietal and perisylvian brain areas (Eden et al., 2004) and effective remediation has shown to partially normalize deficient brain processes during rapid auditory processing in children with developmental dyslexia (Gaab et al., 2007). To summarize, current neuroimaging findings have allowed us to pin-point the neural systems responsible for the acquisition of reading skills and enabled us to gain knowledge in atypical development, such as reading failure. Neuroscience has provided evidence for remediation and it has offered possibilities to detect neural "pre-markers" preceding developmental disabilities, such as the failure to learn to read. An early identification of developmental disabilities, such as dyslexia, may enable early interventions to prevent or minimize any related effects, potentially even before the start of school (Goswami, 2006).

The early detection of children at risk for developmental disabilities may also lead to changes in educational policies, such as the assignment of independent educational plans as well as customized teaching curriculums. An extension of supportive social networks for children and parents of children with developmental dyslexia may lead to a supportive background that

enables an ideal academic and cognitive development. A reduction or even prevention of the clinical, social and psychological consequences of dyslexia is crucial and can lead to a reduction of stress in children and parents with developmental disabilities, ultimately improving overall family and community dynamics.

5.4 A CROSS-LINGUISTIC FACE OF DEVELOPMENTAL DYSLEXIA: UNIVERSAL PRE-MARKERS?

The majority of research on developmental dyslexia derives from English-speaking countries, such as the US, Canada, Australia or the UK (Ziegler et al., 2003). However, various studies performed in European countries suggest that learning to read English might be more difficult and qualitatively different from other orthographies (e.g. (Landerl et al., 1997, Goswami, 2002, Ziegler et al., 2003, You et al., 2011)). One of the crucial milestones during the process of learning to read is the ability to match print to spoken language. Letter-Sound learning is an ability which is learnt at a different rate, depending on the orthography of a given language (for a review see (Goswami, 2002)). Hereby, languages with a consistent alphabetic orthography (such as Italian or Spanish), are less challenging than those with more complex syllables structures (such as German). However, orthographically inconsistent language, such as English are most challenging. In English, one letter may map to different phonemes and so the same spelling patterns can be pronounced differently (Ziegler et al., 2001). As such, the orthography of a given language would determine the level of challenge children face during phonological processing. And in fact, studies have shown that at reading begin, German or Greek dyslexic children display similar difficulties during phonemic segmentation as older English dyslexic children (Wimmer, 1996, Porpodas, 1999). Research has shown that phonemic awareness develops relatively late in orthographically inconsistent languages (Goswami, 2002, Ziegler and Goswami, 2006). Furthermore, depending on what is accentuated in any given language (fluency in German; visual spatial memory in Chinese; phonological skills in English), there may be different phenotypes of dyslexia as well as different predictors for reading ability/failure. In less regular languages (English and French) phonological skills are more important which lead to

phoneme awareness and decoding accuracy as good predictors. Contrariwise, more transparent and more logographic writing systems (e.g. German, Spanish, Finnish, Dutch, Greek, Italian) are dominated by reading fluency and comprehension issues, which lead to processing speed as the best predictor.

When looking at the neural basis of dyslexia converging evidence from various studies done in different countries (e.g. Netherlands, Austria, US and Italy) point to a common neural substrate underlying reading difficulties, such as dyslexia. Independent of language and orthography, individuals with dyslexia seem to show a characteristic network of hypoactivations in temporoparietal and occipitotemporal brain regions (Paulesu et al., 2001, Ziegler et al., 2003) which is complemented by morphological atypicalities in the same areas of the brain. In a study that included individuals with dyslexia from the UK, Italy and France, Paulesu et al. (2001) could show that left temporoparietal disruptions in the functional brain networks of individuals with dyslexia are detectable during explicit and implicit reading tasks, even though the behavioral deficits seem to be constrained by culture. Siok et al. (2004) investigated the neural networks of reading impaired Chinese children and located a functional disruption of the left middle frontal gyrus (Siok et al., 2004)). One possible explanation for the discrepancy in findings may be due to the fact that the English and Chinese writing system fundamentally differ (e.g. Chinese is a logographic rather than alphabetic writing system) and the results underline the importance to critically investigate universal comparisons between languages and challenge the idea of a biological unity theory of dyslexia (Paulesu et al., 2001, Siok et al., 2004). However, a more recent study by You et al. (2011) investigated the neural processes during phonological processing in children with English and Chinese reading impairments compared to tyical reading controls, which resulted in similar neural deficits (reduced activation in posterior dorsal and ventral reading networks).

To summarize, there is behavioral evidence which suggests that even though phonological processing is the most common etiology of dyslexia, the fine grained behavioral face of specific reading disabilities may manifest differently, depending on the language (and orthographic

system) a child grows up in. When looking at neuroimaging findings, converging evidence points towards a characteristic dysfunction of left-hemispheric dorsal and ventral reading networks in individuals with dyslexia across languages. However, most of the neuroimaging studies conducted to date were performed in school-aged children and older. In the current thesis work, we could demonstrate that pre-reading children at risk for dyslexia show neural and structural disruptions in brain areas similar to those seen in children and adults with a diagnosis of dyslexia. Future research will have to determine whether the identified differences may serve as early markers for dyslexia and if so, whether the same is true for pre-reading children of different cultural backgrounds (e.g. Italian-, German-, French-speaking countries). If the orthography of a given language determines the level of challenge children face during phonological processing, then it is possible, that neuronal disruptions (for example during phonological processing) seen in English speaking children end up to be more prominent than those seen in countries with a more shallow orthographic system. This would be in line with studies that have shown that at the start of reading, German or Greek dyslexic children display similar difficulties during phonemic segmentation as older English dyslexic children (Wimmer, 1996, Porpodas, 1999). To conclude, it remains to be investigated whether any neural, behavioral, genetic pre-markers (or any given combination) exist and if so, whether they are universally identifiable or not.

5.5 CONCLUSION

Developmental dyslexia is a specific learning disability with a most likely core deficit in phonological processing. It is highly heritable and one of the best studied developmental disabilities over all. Ample research in adults and children with a diagnosis of developmental dyslexia has revealed atypical brain structure and function in left-hemispheric dorsal and ventral reading networks which go along with reduced (pre-)reading skills. However, when and how this differences manifest remains largely unknown. Through methodological improvements in the field of neuroimaging and by developing a child-appropriate neuroimaging protocol, we were able to perform (f)MRI in 5-year old pre-school children. The present thesis

work lays the foundation for a first line of evidence of structural, functional and behavioral disruptions in children with a family-history of dyslexia before reading onset. Comparing children at risk for dyslexia (family-history) to those without enabled us to gain understanding of characteristic markers in the development of dyslexia present prior to reading onset. This data furthermore informs about the development of reading networks in the typical and atypical developing child. Since all children tested here were still pre-readers, any observed structural and functional brain alterations in children at risk for dyslexia cannot be due to reading failure per se, but most likely develops during the first few years of life or may already be present at birth. Further studies employing longitudinal designs will have to determine whether and how the observed structural, functional and behavioral differences in children at risk for developmental dyslexia may serve as early markers for reading disabilities. The identification of early pre-markers of dyslexia in pre-reading children is essential for the development and improvement of early intervention programs and may prevent the clinical, psychological and social impact associated with developmental dyslexia.

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7 APPENDIX

7.1 SUPPLEMENTARY MATERIAL TO **STUDY 4**

		FHD+	FHD-	P-Values Sig. 2-tailed
		Mean ± SD	Mean ± SD	FHD+ vs. FHD-
N		18	18	
Age (in months / psychometrics session)		68.06 ± 4.95	66.58 ± 4.44	0.355
Age (in months / imaging session)		69.61 ± 4.76	70.99 ± 6.38	0.466
Behavioral Measures				
CELF	Core Language	101.83 ± 11.18	109.00 ± 9.80	0.049 *
	Receptive Language	105.11 ± 13.49	108.11 ± 11.41	0.476
	Expressive Language	98.33 ± 9.98	108.61 ± 10.32	0.005 **
	Language Content	102.22 ± 11.23	108.78 ± 11.46	0.092
	Language Structure	100.50 ± 12.43	108.72 ± 9.90	0.035 *
CTOPP	Elision [b]	8.76 ± 1.09	10.33 ± 2.45	0.021 *
	Blending [b]	10.29 ± 1.93	11.44 ± 1.62	0.064
	Non-Word Repetition [b]	9.94 ± 2.14	10.33 ± 2.22	0.598
RAN	Objects [a]	89.83 ± 12.99	104.35 ± 12.07	0.002 **
	Colors [b]	92.82 ± 15.17	105.06 ± 12.78	0.014 *
VATT	Inflection [c]	23.19 ± 9.73	25.37 ± 8.64	0.506
	Repetition [c]	32.81 ± 9.01	38.38 ± 1.96	0.022 *
KBIT	Verbal Ability [a]	111.72 ± 8.77	110.76 ± 8.07	0.739
	Non-Verbal Ability [a]	98.89 ± 7.19	101.82 ± 12.20	0.389
In-Scanner Performance				**sig. 2-tailed** *Independent samples t-test*
		Mean ± SD	Mean ± SD	
FSM [a]	Correct	13.83 ± 3.76	21.06 ± 5.14	0.000 ***
	Incorrect	10.89 ± 3.08	5.06 ± 4.53	0.000 ***
	Missed	3.28 ± 2.78	1.88 ± 2.03	0.101
Socioeconomic Status		**Mean ± SD**	**Mean ± SD**	**sig. 2-tailed** *Independent samples t-test*
Parental Education [d]		6.03 ± 0.76	6.19 ± 0.79	0.522
		Mean Rank	**Mean Rank**	**sig. 2-tailed** *Mann-Whitney*
Income (total family income for last 12 months) [e]		15.08	11.92	0.251

* P < .05; ** P < .01; *** P < .001; two-tailed t-test;
all other t-tests non-significant at threshold of P = .05

Measures (standard scores are reported)

[a] 18 FHD+/17 FHD- (One child did not finish all testing)

[b] 17FHD+/18 FHD- (One child did not finish all testing)

[c] 16FHD+/16 FHD- (Four children did not finish all testing)

[d] Parental Education scores are calculated according to the 7-point Hollingshead Index Educational Factor Scale, summed for husband and wife and divided by two (Hollingshead, 1975).

[e] Scale where 1 = 0 - 5,000 $, 2 = 5,000 - 11,999 $, 3 = 12,000 - 15,999 $, 4 = 16,000 - 24,999 $, 5 = 25,000 - 34,999 $,

Supporting Information 1. Subject Demographics.

SI1. Socioeconomic characteristics (SES) of children with (FHD+) and without (FHD-) a family history of dyslexia.

		FHD+	FHD-	*p*
		[%]	[%]	**sig. 2-tailed** *Mann-Whitney test*
Mother Characteristics (%)				
Education (highest degree earned)	High School Diploma/GED	11.00%	0.00%	0.791
	Associate Degree	0.00%	0.00%	
	Bachelor's Degree	33.30%	52.92%	
	Master's Degree	49.00%	35.28%	
	Doctorate	0.00%	5.88%	
	Professional(MD, JD)	5.55%	0.00%	
	OtherSpecify	0.00%	0.00%	
	No Response	0.00%	5.88%	
Current activity	Working Full Time	16.50%	17.64%	0.801
	Working Part Time	33.30%	17.64%	
	Unemployed or laid off	0.00%	0.00%	
	Looking for work	11.00%	0.00%	
	Staying At Home, raising a child	38.50%	64.68%	
	Retired	0.00%	0.00%	
	No Response	0.00%	0.00%	
Money earned within the last 12 months	Less Than $5000	44.40%	47.04%	0.767
	$5,000-$11,999	5.55%	5.88%	
	$12,000-$15,999	5.55%	0.00%	
	$16,000-$24,999	0.00%	0.00%	
	$25,000-$34,999	0.00%	0.00%	
	$35,000-$49,000	0.00%	5.88%	
	$50,000-$74,999	5.55%	11.76%	
	$75,000-$99,999	0.00%	5.88%	
	$100,000 and Greater	22.20%	5.88%	
	Don't know	0.00%	0.00%	
	No Response	16.65%	17.64%	
Home owner status	Home Rented for Money	11.10%	17.64%	0.586
	Home Owned By You	88.80%	82.32%	
	Home Owner Status Not Available	0.00%	0.00%	

Family Characteristics (%)				
Money earned within the last 12 months	Less Than $5000	0.00%	0.00%	0.383
	$5,000-$11,999	5.55%	5.88%	
	$12,000-$15,999	0.00%	0.00%	
	$16,000-$24,999	0.00%	0.00%	
	$25,000-$34,999	0.00%	0.00%	
	$35,000-$49,000	0.00%	0.00%	
	$50,000-$74,999	27.50%	5.88%	
	$75,000-$99,999	0.00%	23.52%	
	$100,000 and Greater	66.60%	52.92%	
	Don't know	0.00%	0.00%	
	No Response	0.00%	11.76%	
Length of time you could maintain standard of living if all income is lost				
	Less than 1 Month	11.11%	5.88%	0.345
	1-2 Months	16.50%	11.76%	
	3-6 Months	44.40%	35.28%	
	7-12 Months	11.50%	29.40%	
	More Than 1 Year	16.50%	5.88%	
	No Response	0.00%	11.76%	

* P < .05; two-tailed t-test; all other t-tests non-significant at threshold of P = .05

SI2. Home Literacy Envrionment (HLE) of children with (FHD+) and without (FHD-) a family history of dyslexia.

		FHD+	FHD-	*p*
		[%]	[%]	sig. 2-tailed
Total number of parents/adult books in the home	0-50	14.29	20.00	0.748 [a]
	50-100	21.43	6.67	
	100+	64.29	73.33	
Total number of children's books in the home	0-50	85.71	0.00	0.136 [a]
	50-100	7.14	0.00	
	100+	7.14	100.00	
Age (in months) of child when first read to		2.2	6.9	0.291 [b]
[mean in month]				
Amount of time at home that someone reads to the child		2.6	3.6	0.200 [b]
[hours/week]				
How often do family members read books, magazines or newspapers with the child?	1-2	0.00	6.67	0.935 [a]
[times/week]	3-4	7.14	0.00	
	5-6	28.57	26.67	
	daily	64.29	60.00	
	N/A		6.67	
How often do family members teach the child how to write?	1-2	21.43	33.33	0.428 [a]
	3-4	35.71	26.67	
[times/week]	5-6	21.43	33.33	
	daily	21.43		
	N/A		6.67	
How often do family members teach the child to count?	1-2	7.14	13.33	0.268 [a]
	3-4	28.57	46.67	
[times/week]	5-6	35.71	6.67	
	daily	28.57	20.00	
	N/A		13.33	

How often do family members help the child with their school work?	1-2	7.14	13.33	0.324 [a]
[times/week]	3-4	21.43	33.33	
	5-6	42.86	33.33	
	daily	28.57	13.33	
	N/A		6.67	
How often do family members teach the child to read words?	1-2	7.14	13.33	0.316 [a]
[times/week]	3-4	0.00	13.33	
	5-6	28.57	20.00	
	daily	64.29	46.67	
	N/A		6.67	
How often does the child ask someone to read to them?	1-2	7.14	13.33	0.554 [a]
	3-4	28.57	20.00	
[times/week]	5-6	0.00	13.33	
	daily	64.29	46.67	
	N/A		6.67	
How often does someone at home help the child with their homework in reading and writing?	1-2	28.57	20.00	0.364 [a]
	3-4	14.29	46.67	
[times/week]	5-6	35.71	20.00	
	daily	21.43	6.67	
	N/A		6.67	
How often does the child look at books at home by themselves?	1-2	14.29	13.33	0.821 [a]
[times/week]	3-4	21.43	20.00	
	5-6	14.29	6.67	
	daily	50.00	53.33	
	N/A		6.67	
How often do family members read newspapers, books or magazines?	1-2	0.00	6.67	0.535 [a]
[times/week]	3-4	7.14	13.33	
	5-6	7.14	73.33	
	daily	85.71	0.00	
	N/A		6.67	

Supporting Information 4

Text S1

Methods

Participants. During an initial telephone-/email-screening with the parents we screened for pre-reading status in all children. Only pre-reading children (parent report) who planned to enter kindergarten in the following few weeks were invited to take part in the study. Furthermore, the word ID subtest of the Woodcock Reading Mastery Test (WRMT; (1)) was administered to all children. Twenty-four children were unable to read one sight word (11FHD+/13FHD-), nine children (4FHD+/5FHD-) recognized one to two words, and three children (FHD-) recognized three to four isolated sight words. Data obtained in the national early childhood longitudinal study (ECLS-K, kindergarten class of 1998-1999), indicate that by kindergarten entry only 2 % of all children in the United States are able to identify sight words and no more than 1% recognize words in context (2).

fMRI – Acquisition. For each run (experimental and control task), 56 functional whole-brain images were acquired with a 32 slice EPI interleaved acquisition on a SIEMENS 3T Trio MR scanner including the following specifications: TR 6000 ms; TA 1995ms; TE 30 ms; flip angle 90°; field of view 256 mm; voxel size 3 × 3 × 4 mm, slice thickness 4mm. Prior to the start of the first block, additional functional images were obtained and later discarded to allow for T1 equilibration effects. Stimuli were presented using Presentation® software (Version 0.70, www.neurobs.com). The complete imaging session included 2 additional functional imaging tasks and lasted about 1.5 hours with breaks, following a 45 minute preparation session in the mock scanner area.

fMRI - Task Procedure. Each child performed two consecutive fMRI runs: one with the experimental task and one with the control task. Based on experience gained from a preliminary pilot study, the two tasks were presented in separate runs in order to avoid confusion in our youngest participants (age range 62.2-81.6 months). The design (including timing and duration; see **Figure S1**) of these two tasks were identical and the order of the runs was pseudo-randomized across children. During the first four seconds of each trial, the child listens to two words (two seconds per word). This is followed by a question mark displayed for two seconds (**Figure S1**).

During the experimental run, children performed a phonological processing task which involved listening to two subsequently presented common object words spoken in a female or male voice via MR-compatible noise-reducing headphones. Pictures were presented on the screen simultaneously in order to engage the children and to reduce working memory demands (**Figure S1**). Using two child-friendly buttons that were placed on either side of the participant, children were asked to indicate via button-press whether the two words presented started with the same first sound (e.g. *bed* and *belt*; "yes") or not (e.g. *bird* and *ant;* "no"). This task was contrasted with a rest condition. During the rest condition, children were asked to look at a fixation cross for the duration of the block. This task is an adapted and modified version from the Sound-Matching task presented by Katzir and colleagues (3).

The control task also involved listening to two common object words spoken in a female or male voice. Mirroring the experimental task, pictures that illustrate the spoken words were presented on the screen simultaneously (**Figure S1**). Participants were asked to indicate by button-press whether or not the gender of the voice matched for the two words presented. This task was also contrasted with a rest condition.

All words between experimental and control task were matched for age of acquisition (<4 years), Brown verbal frequency, concreteness, imagery, numbers of letters, numbers of phonemes and numbers of syllables (MRWC Psycholinguistic and the IPNP Database; http://www.psy.uwa.edu.au/mrcdatabase/uwa_mrc.html and http://crl.ucsd.edu/~aszekely/ipnp/). All pictures are adapted from the standardized Snodgrass Picture System (4).

A behavioral interleaved gradient imaging design (BIG) allowed for the presentation of the auditory stimuli without scanner background noise interference (5-8). A total of seven blocks of the experimental/control condition and seven blocks of the rest condition with an overall duration of 336s seconds for each run (experiment and control) was employed. Each block lasted 24 seconds, and each block contained four trials. In experimental and control tasks, 50% of all items matched regarding their first sound and 50% of the words were spoken in a male/female voice. The trials were distributed over the course of seven blocks, during 5 blocks 50% of the answers were match/non-match, during two blocks one respectively three trials were match/non-match. The order of trials within a block was randomized.

Each child underwent extensive preparation and training in the mock MR scanner area before the actual neuroimaging session. Participants were familiarized with the experimental and control tasks prior to the neuroimaging session using unique practice items. Instructions for each task were presented in separate short videos which were shown in the MR scanner area and repeated prior to actual scanning. To reduce movement during the scanning procedure, cushions were used to stabilize the head and response buttons were placed at arm's length on each side of the child. A member of the research team observed the child during in-scanner performance and provided a tactile reminder to stay still during the session if needed (for a detailed description of the training protocol see (9)).

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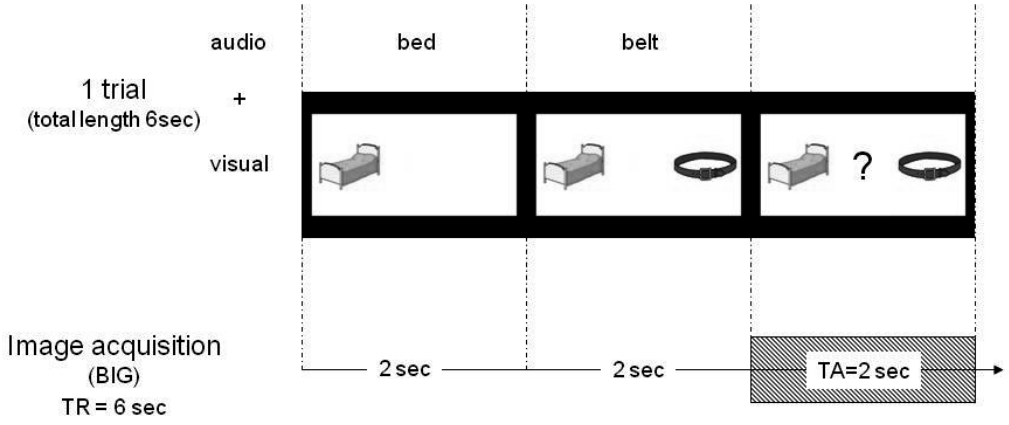

7.2 SUPPLEMENTARY MATERIAL TO **STUDY 5**

SI1. Socioeconomic characteristics (SES) of children with (FHD+) and without (FHD-) a family history of dyslexia.

		FHD+	FHD-	*p*
		[%]	[%]	**sig. 2-tailed** *Kruskal Wallis test*
Mother Characteristics (%)				
Education (highest degree earned)	College School	0	0	
	Graduate School (Bachelor's Degree)	44.44	60	
	Graduate School (Master's Degree)	55.55	40	0.509
Current activity	Working Full Time	11	20	
	Working Part Time	33	20	
	Staying At Home	56	60	1.000
Money earned within the last 12 months	No Response	33	40	0.275
	Less Than $5000 Earned in Past 12 Months	33	30	
	35,000-49,000 Earned in Past 12 Months	11	10	
	50,000-74,999 Earned in Past 12 Months	0	10	
	75,000-99,999 Earned in Past 12 Months	0	10	
	100,000 and Greater Earned in Past 12 Months	22	0	
Home owner status	Home Rented for Money			1.000
	Home Owned By You	100	90	
	Home Owner Status Not Available	0	10	
Family Characteristics (%)				
Money earned within the last 12 months	No Reponse	0	20	0.865
	50,000-74,999 Earned in Past 12 Months	22	0	
	75,000-99,999 Earned in Past 12 Months	11	30	
	100,000 and Greater Earned in Past 12 Months	67	50	
Length of time you could maintain standard of living if all income is lost	No Response	0	20	
	Less than 1 Month	0	10	
	1-2 Months	0	10	
	3-6 Months	33	30	
	7-12 Months	44	20	
	More Than 1 Year	22	10	0.363

* P < .05; two-tailed t-test; all other t-tests non-significant at threshold of P = .05

N=19 (one family did not fill out the questionnaire)

SI2. Home Literacy Envrionment (HLE) of children with (FHD+) and without (FHD-) a family history of dyslexia.

		FHD+	FHD-	*p*
		[%]	[%]	sig. 2-tailed
Total number of parents/adult books in the home	0-50	22.22	33.33	0.844 [a]
[%]	50-100	22.22	11.11	
	100+	55.55	55.55	
Total number of children's books in the home	0-50	11.11	0	0.146 [a]
[%]	50-100	11.11	0	
	100+	77.77	100	
Age (in months) of child when first read to		4.37	9.77	0.429 [b]
[mean in month]				
Amount of time at home that someone reads to the child		2.66	3.43	0.28 [b]
[hours/week]				
How often do family members read books, magazines or newspapers with the child?	1-2	0	0	0.385 [a]
[times/week]	3-4	11.11	0	
	5-6	44.44	33.33	
	daily	44.44	55.55	
	N/A	0	11.11	
How often do family members teach the child how to write?	1-2	22.22	11.11	0.458 [a]
	3-4	55.55	44.44	
[times/week]	5-6	0	0	
	daily	22.22	33.33	
	N/A	0	11.11	
How often do family members teach the child to count?	1-2	22.22	11.11	0.783 [a]
	3-4	22.22	44.44	
[times/week]	5-6	33.33	0	
	daily	22.22	22.22	
	N/A	0	22.22	
How often do family members teach the child the alphabet?	1-2	22.22	44.44	0.186 [a]
[times/week]	3-4	22.22	11.11	
	5-6	22.22	11.11	

8 CURRICULUM VITAE

PERSONAL DATA

Name and Address	Raschle Nora Maria	Swiss address:	Raschle Nora Maria
	3 Clark Street		c/o B. & S. Schnider
	Unit B		Im Zentrum 2b
	Somerville, MA 02143 (USA)		9300 Wittenbach (CH)
Phone	++1 617 515 9149		++41 71 988 56 13
E-Mail	nora.raschle@childrens.harvard.edu / nora.raschle@gmail.com		
Date of Birth	November 4th, 1981		
Marital Status	married	Name at Birth:	Schnider Nora Maria

EDUCATION

Eidg. Matura Typus C	Kantonsschule Wattwil, Switzerland	1996- 2000

Basic studies in Psychology at the University of Zurich 2001 – 2003

Master studies in Neuropsychology 2004 – 2007

(at the Department of Neuropsychology, University of Zurich); Final exams in general psychology, applied psychology, clinical psychology, social psychology as well as the following minor subjects:

1. Minor subject: Psychopathology

2. Minor subject: Social- & Preventive Medicine

Diploma thesis	2006
Music & Neuroimaging Laboratory of Prof. Schlaug (Beth Israel Deaconess Medical Center and Harvard Medical School in Boston, USA); supported by Prof. Jäncke (Department of Neuropsychology, University of Zurich, Switzerland): „Modulating pitch-memory performance through transcranial direct current stimulation“	

Master of Science	University of Zurich, Switzerland	2001 – 2007

PhD student	University of Zurich (Switzerland)	2008 – present
	Children's Hospital & Harvard Medical School Boston, MA (USA	

WORK EXPERIENCE

Neuropsychological internship at the Rehabilitation Clinic Zihlschlacht	2003 / 3 months
Psychological Internship, PUK Basel	2004 / 2 months
Research trainee at the Music & Neuroimaging Laboratories of the Beth Israel Deaconess Medical Center & Harvard Medical School, Boston (USA)	2005 / 6 months
Visiting Fellowship Program in Functional MRI at the Martinos Center for Biomedical Imaging, Boston (USA)	2008 / October 6-10

FUNDING SOURCES

2008/2009	01/01/ 2008- 12/31/ 2009	Swiss National Foundation. NICHD (RO1 HD65762-01)
2010/2011	01/01/2010-09/31/2011	Janggen Poehn Stiftung

PUBLICATIONS

PAPER

Vines, B.W., Schnider, N.M. & Schlaug, G. (2006) Testing for causality with transcranial direct current stimulation: pitch memory and the left supramarginal gyrus. *Neuroreport 17* (10), 1047-50.

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Raschle, N.M., Stering, P., & Gaab, N. (2010). Disruptive neural response during rapid auditory processing in pre-readers at risk for dyslexia - an fMRI study. Accepted for oral presentation at the *Society for Developmental and Behavioral Pediatrics (SDBP) 2010* Annual Meeting, Boston (USA)

Raschle, N.M., Stering, P.L. & Gaab, N. (2010). Disruptive neural response during rapid auditory processing in pre-readers at risk for dyslexia – an fMRI study. Oral presentation for the Annual Meeting of the *Society for Developmental and Behavioral Pediatrics, Boston*, MA; September, 2010.